MEDICATION ERRORS AND ADVERSE DRUG EVENTS IN HOSPITALISED PATIENTS; METHODOLOGICAL ISSUES AND COMPUTERISED INTERVENTION

Jasperien E. van Doormaal

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Stellingen behorende bij het proefschrift

Medication errors and adverse drug events in hospitalised patients; methodological issues and computerised intervention

1. Het elektronisch voorschrijfsysteem is een stap in de richting van een patiëntveilige omgeving.
(Dit proefschrift)

2. Het beoordelen van voorkombare geneesmiddelschade laat altijd ruimte over voor een subjectieve interpretatie van de beoordelaar.
(Dit proefschrift)

3. "We do not know a truth without its cause"
(Aristoteles, 350 voor Christus)

4. Hoewel de administratieve medicatiefout niet geassocieerd is met patiëntschade leidt hij zorgverleners wel af van het primaire zorgproces en is daarom niet ongevaarlijk.
(Dit proefschrift)

5. De randomised controlled trial is een gouden standaard voor de interventiestudie maar een interrupted time-series design is een goed zilveren alternatief.

6. Clinical rules should be considered as tools and not as rules.

7. Voor het implementeren van een elektronisch voorschrijfsysteem in een groot academisch ziekenhuis is het hebben van geduld een eerste vereiste.

8. De extra kosten om met het elektronisch voorschrijfsysteem een medicatiefout te voorkomen ten opzichte van het handgeschreven systeem zijn te verwaarlozen in vergelijking met andere kosten in de gezondheidszorg.
(Dit proefschrift)

9. Problemen met het implementeren van een elektronisch voorschrijfsysteem liggen op een ander vlak dan weerstand tegen verandering.
(Dit proefschrift)

10. "Soms is wat onmogelijk lijkt, alleen maar moeilijk"
(De engelenmaker, Stefan Brijs)

11. Als promovendus zit je gevangen in een spinnenweb van belangen.

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Contents

Introduction

Part 1: Methodological aspects of medication errors and adverse drug events

World-wide many patients suffer from drug related problems of which a large part is preventable. Already in 1969 Hurwitz et al. published the article 'Intensive Hospital Monitoring to Adverse Reactions to Drugs' in the British Medical Journal.[1] She showed that 10 % of the hospitalised patients in the UK suffered from harm due to medication. Her findings were comparable to the results of earlier studies in the sixties.[2-4] These research findings led to an increased awareness in the UK concerning medication related harm. Thirty years later the US report 'To Err is Human' showed that many people died each year in hospitals partially due to medication related harm often caused by medication errors.[5] Again awareness and anxiety increased and since then improving medication safety has been high on the agenda of health care providers in the United States as well as in European countries (e.g. the Netherlands). This has resulted in a number of studies looking into the frequency and preventability of drug related problems in hospitalised patients. In their literature review Krähenbühl-Melcher *et al.*[6] concluded that overall in about 6% of the hospitalised patients medication related harm occurs of which about half is preventable and can be considered the result of medication errors. The same percentages are mentioned for the frequency and preventability of hospital admissions due to medication in for example the UK[7] (6.5 % medication related admissions of which 72% avoidable) and the Netherlands[8, 9] (approximately 5% medication related admissions of which around 40% potentially avoidable). These findings indicate the scope of drug related problems in hospitals.

For a further exploration of these problems and their causes a good understanding of the terminology is needed. Drug related problems are defined as circumstances involving a patients' drug treatment, that actually or potentially interfere with the achievement of an optimal outcome.[10, 11] These problems include medication errors, adverse drug reactions and adverse drug events. The definitions of these terms and their relationship are presented in **Table** 1 and graphically displayed in **Figure 1.**

Adverse drug events are injuries related to the use of a drug, although the causality of this relationship may not be proven.[12] Adverse drug events include adverse drug reactions which are not preventable, but also injuries which are related to medication errors and thus are preventable – preventable adverse drug events. So, in terms of improving medication safety interventions should focus on drug related problems that are preventable, i.e. medication errors and preventable adverse

drug events. A substantial number of studies have performed into the nature and rates of medication errors in the hospital setting.[6, 11, 13-15] However, from a clinical point of view preventable adverse drug events are more relevant as outcome measures because not all medication errors do cause patient harm.

Table 1: definitions of drug related problems

Medication error	Any error in the process of prescribing, dispensing or administering of a drug whether there are adverse consequences or not.[12]
Adverse drug event	An injury related to the use of a drug, although the causality of this relationship may not be proven.[12]
Adverse drug reaction	A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function[29]
Preventable adverse drug event	Injury that is the result of an error in any stage in the medication use[17]

Studies use different methods for identifying adverse drug events (non-preventable as well as preventable); spontaneous reporting by patients or health care professionals[16], interviewing patients[17], studying electronical databases[18], using computerised trigger tools[19] and chart review.[20] This variety of methods – and the sometimes different definitions used - leads to a high variability in the rates of adverse drug events found in medication safety studies.[6] All these methodologies have strengths and limitations. A limitation of spontaneous reporting is underreporting of adverse drug events, on the one hand due to lack of willingness to report an adverse drug event and on the other hand due to lack of awareness of an adverse drug event.[21] In contrast, a limitation of interviewing patients is the low positive predictive value for detecting true adverse drug events because of bias, .i.e. patients come up with many disease related events.[22] Screening electronic databases is helpful because of the availability of clear and structured data. However a disadvantage is the restriction to data that can only be entered in the strict format of the database. Applying computerised trigger tools on patient data may play an important role in future because it may be time-saving. However, these tools should be further developed to decrease the false positive signals they generate. The main benefit of chart review in comparison to the other methods is that it usually gives a large amount of rather objective and detailed data. Furthermore, Jha *et al.*[23] showed

that chart review detected more adverse drug events in comparison to computer monitoring or spontaneous reporting and it was more effective in detecting preventable adverse drug events. Therefore, chart review can be considered as the best approach so far in methodologies for identifying adverse drug events.
Chart review as a method to identify preventable adverse drug events has two

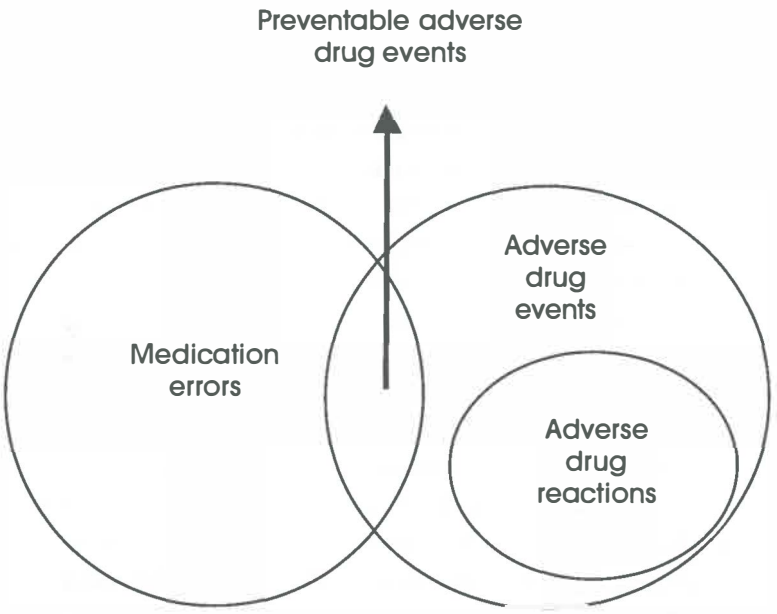

Figure 1: relationship between different drug related problems

limitations. First, it is labour intensive and therefore costly. Secondly, physicians and nurses notice many patients' symptoms and clinical events but do not link them to drugs or when they suspect a link they usually do not note this presumption. Therefore researchers need to assess the association between drugs, medication errors and adverse drug events by themselves. For the assessment of (non-preventable) adverse drug reactions, i.e. the assessment of the link between a drug and an adverse drug event, the agreement is often not very high between individual assessors.[24-26] In an attempt to increase agreement, various instruments (e.g. sets of questions and algorithms) have been developed to assess the causality between an adverse event and medication use in a systematic way, such as the method of Naranjo[27] or the algorithm of Kramer[28]. These instruments focus on the assessment of adverse drug reactions, however not on preventable adverse drug events. For identifying preventable adverse drug events actually two assessments should be performed; one for the relation between a drug and a medication error and second for the relation between a medication error and an adverse drug event. This

combined systematic approach has not been used previously in studies looking into preventable adverse drug events. In **chapter 2** of this thesis this approach was tested in panels of pharmacists and physicians.

In general, there are two types of medication safety studies. One type of studies focuses on the characteristics of medication errors and adverse drug events, such as the classification of errors/adverse drug events, determinants of errors/adverse drug events and the relation between medication errors and adverse drug events. The other type of studies are intervention studies that focus on interventions and strategies to reduce the incidences of medication errors and/or adverse drug events, e.g. that study the effect of computerised prescribing or the effect of education for physicians or pharmacists. In order to develop interventions that will improve medication safety, the characteristics of medication errors and adverse drug events should be explored first. Knowledge on the most clinically relevant medication errors at which interventions should be directed, is important. Studies of characteristics of medication safety problems offer the opportunity to specify types of medication errors associated with adverse drug events enabling future studies and interventions to focus more on these types of errors. For the same reason it is important to explore whether determinants of errors are the same as determinants of adverse drug events. Interventions can then focus on those determinants. This information is relevant because methods for identifying medication errors and adverse drug events are very labour intensive. In **chapter 3** and **chapter 4** we explored the clinical relevance of errors and determinants further. **Chapter 3** focused on which types of medication error are mostly associated with adverse drug events and are therefore most clinically relevant. **Chapter 4** investigated whether the determinants of medication errors that do not cause any patient harm are the same as determinants of medication errors that do cause patient harm.

Part 2: Computerised Physician Order Entry system with Clinical Decision Support (CPOE/CDSS) in relation to medication safety

Until recently the medication distribution process in Dutch hospitals was based on hand-written information where medication orders were written on paper charts by physicians and thereafter transcribed to drug administration charts by nurses. In some hospitals the pharmacy took care of central order entry, but not in all. Hospitals without central order entry also lacked systematic medication review of medication orders by pharmacists. In general, no immediate clinical decision support was present (e.g. warnings on drug - drug interactions and drug overdoses) for the physicians during prescribing. Even in central order entry hospitals this was lacking. Omission of these last two aspects combined with the fact that the system was based on hand-writing, was a potential source for the occurrence of medication errors and preventable adverse drug events.

Since the publication of 'To Err is Human' many strategies to make health care safer have been created and meanwhile implemented. One of these strategies is the Computerised Physician Order Entry (CPOE) system. Before the first introduction of this system in the United States in the nineties, expectations about CPOE systems reducing medication errors and preventable adverse drug events were high. These computerised systems would standardise the medication ordering process. Legible and complete orders would be ensured.[30] Furthermore, Clinical Decision Support systems (CDSS) would be incorporated in these CPOE systems which could assist the physicians by triggering alerts in case of drug-drug interactions and inappropriate dosing. Pharmacists could check alerts that were neglected by the physicians. Because of Clinical Decision Support Systems and the production of legible standardised orders, CPOE/CDSS systems promised to reduce medication errors (especially regarding prescribing and transcribing) and preventable adverse drug events. Meanwhile, a number of studies (predominantly from the US) have shown that CPOES/CDSS systems may be a successful strategy in reducing medication errors[31-33] as well as preventable adverse drug events.[34, 35] Other studies showed negative effects in the sense that new medication errors were being introduced by CPOE/CDSS [36] or that mortality increased after implementation of CPOE/CDSS in a children's hospital.[37] A problem with most studies is that the findings of these studies cannot be considered robust because of a weak study design. Moreover the majority of these studies were from the United States where CPOE/CDSS was first introduced. Europe differs from the United States and here other types of CPOE/CDSS are used. It is important to know what the effect of CPOE/CDSS is on medication safety in the European setting. In **chapter 5** of this thesis we evaluated the effect of CPOE/CDSS on the incidence of medication errors and preventable adverse drug events in two Dutch hospitals.

CPOE/CDSS is a first step in the computerization of the prescribing process. It offers the possibility of extensive support systems at the point of care that facilitate better and safer medication use. Currently CDSS in CPOE systems is relatively basic[38], i.e. it provides only support on dosages, drug-drug interactions, duplicate therapy and allergies. More advanced decision support such as support on dosages for patients with renal or liver failure, support on drug choice for specific patients or support on therapy for patients with specific risk factors may further help to reduce medication errors and preventable adverse drug events. At present some hospitals in the Netherlands are developing more advanced decision support. Clinical rules are defined that are basically computerised algorithms that look for specific medication orders, patient characteristics and/or laboratory values that could lead to patient harm.[39] These clinical rules will select hospitalised patients who are at risk for suffering from an adverse drug event. Based on this selection, health care professionals can intervene before actual patient harm will occur. The development of these clinical rules is still in progress and several aspects should be explored further before implementation in clinical practice can take place. For example; who will be the receivers of the information that clinical rules will generate, pharmacists or physicians? What is the best way of developing a validated clinical rule that is supported by all health care professionals? What is the sensitivity of the clinical rules to prevent adverse drug events, i.e. do these rules select all patients that are at risk? And what is the efficiency of the clinical rules to prevent adverse drug events, i.e. do they not generate too many alerts that need no clinical action? In **chapter 6** of this thesis we address the efficiency of a small set of clinical rules to prevent medication errors and thus finally adverse drug events.

The development and validation of computer technology is one thing, however it has to be implemented effectively in clinical practice before it can have any effect. The introduction of CPOE/CDSS on the workfloor will affect clinical practice in the sense that the workflow of health care professionals will change as well as the communication between them.[40-42] Therefore for a successful implementation, it is important to know the expectations and experiences of (future) users, i.e. physicians and nurses. Knowing the views of users towards this system may lead to improvements of the system and help to fit in clinical practice. In **chapter 7** of this thesis we explored the expectations and experiences with CPOE/CDSS of physicians and nurses in a survey study. Besides the effectiveness of CPOE/CDSS for preventing medication errors and preventable adverse drug events, the aspect of costs is an important issue. Organisations contemplating the implementation of CPOE/CDSS benefit from information on the cost-effectiveness of these technologies in comparison to the traditional methods used before. Introduction and maintenance of CPOE/CDSS is costly[43] and it is important to know whether the ratio between costs and prevented medication errors or adverse drug events is

acceptable. At present, limited information is available on the cost-effectiveness of these systems. The few available studies generally show high cost-effectiveness ratios. [43, 44] However, differences in study design, measures of effect, setting and health care system, limit the generalisability of these results. For the Dutch situation no previous studies have been performed. In **chapter 8** of this thesis we performed an economic evaluation into the cost-effectiveness of CPOE/CDSS in comparison to the paper-based system of medication ordering.

In this thesis we studied the implementation of CPOE/CDSS in two hospitals in the Netherlands, taking into account methodological issues, effectiveness in preventing medication errors and adverse drug events as well as the cost-effectiveness of CPOE/CDSS in comparison to the traditional paper based system.

Outline of this thesis

In **chapter 1** of this thesis we introduced the main objectives of this thesis.
This thesis covers two parts:

PART 1 of this thesis focuses on the methodological aspects of medication errors and adverse drug events:

- In **chapter 2** the focus is on the assessment of the relation between medication errors and adverse drug events. In this chapter we evaluate the agreement on assessing preventable adverse drug events between different professionals, i.e. physicians and pharmacists.
- In **chapter 3** the relation between different subtypes of medication errors and patient harm is assessed in depth. We address which type of medication errors is mostly related to adverse drug events and is therefore most relevant from a clinical perspective.
- In **chapter 4** we assess whether the determinants of medication errors not related to any patient harm are the same as medication errors related to patient harm.

PART 2 focuses on CPOE/CDSS in relation to medication safety:

- **Chapter 5** discusses the effect of the introduction of CPOE/CDSS on the incidence medication errors and preventable adverse drug events in two Dutch hospitals. We distinguish the effect on different types of medication errors and preventable adverse drug events.
- In **chapter 6** we focuses on the different forms of decision support during electronic prescribing. We compare two computerised systems (a basic CDSS within a CPOE and a set of clinical rules) with medication review to answer the question to what extent patients at risk for medication related harm as identified by

the two computerised systems actually have a medication error as identified by medication review.

- Because the effectiveness of the CPOE/CDSS system in reducing medication errors depends also on the use of CPOE/CDSS by health care professionals, we surveyed the expectations and experiences with the system of physicians and nurses. These results are shown in **chapter 7**.
- Currently, in most Dutch hospitals CPOE/CDSS is already used or will be implemented in the coming future. It is important to know what should be extra invested to increase medication safety by using CPOE/CDSS. **Chapter 8** aims to evaluate the balance between the effects and costs of CPOE/CDSS compared to the paper-based system.

References

(1) *Hurwitz N, Wade OL. Intensive hospital monitoring of adverse reactions to drugs. BMJ 1969 March 1;1(5643):531-6.*

(2) *Hoddinott BC, Gowdey CW, Coulter WK, Parker JM. Drug reactions and errors in administration on a medical ward. Can Med Assoc J 1967 October 21;97(17):1001-6.*

(3) *Schimmel EM.. The hazards of hospitalization.. Ann Intern Med 1964 January;60:100-10.*

(4) *Ogilvie RI, Ruedy J. Adverse drug reactions during hospitalization. Can Med Assoc J 1967 December 9;97(24):1450-7.*

5) *To Err is Human: Building a Safer Health System. Washington, DC: National Academy Press; 1999.*

(6) *Krahenbuhl-Melcher A, Schlienger R, Lampert M, Haschke M, Drewe J, Krahenbuhl S. Drug-related problems in hospitals: a review of the recent literature. Drug Saf 2007;30(5): 379-407.*

(7) *Pirmohamed M, James S, Meakin S et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 2004 July 3;329(7456):15-9.*

(8) *Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med 2008 September 22;168(17):1890-6.*

(9) *van der Hooft CS, Dieleman JP, Siemes C et al. Adverse drug reaction-related hospitalisations: a population-based cohort study. Pharmacoepidemiol Drug Saf 2008 April;17(4):365-71.*

(10) *Johnson JA, Bootman JL. Drug-related morbidity and mortality. A cost-of-illness model. Arch Intern Med 1995 October 9;155(18):1949-56.*

(11) *Bemt van den PMLA, Egberts ACG. Drug-related problems: definitions and classifications. EJHP 2006;12((suppl.)):10-2.*

(12) *Leape LL. Preventing adverse drug events. Am J Health Syst Pharm 1995 February 15;52(4):379-82.*

(13) *Devine EB, Wilson-Norton JL, Lawless NM et al. Characterization of prescribing errors in an internal medicine clinic. Am J Health Syst Pharm 2007 May 15;64(10):1062-70.*

(14) *Dean B, Schachter M, Vincent C, Barber N. Prescribing errors in hospital inpatients:*

their incidence and clinical significance. Qual Saf Health Care 2002 December;11(4):340-4.

(15) Lisby M, Nielsen LP, Mainz J. Errors in the medication process: frequency, type, and potential clinical consequences. Int J Qual Health Care 2005 February;17(1):15-22.

(16) Al Tajir GK, Kelly WN. Epidemiology, comparative methods of detection, and preventability of adverse drug events. Ann Pharmacother 2005 July;39(7-8):1169-74.

(17) Morimoto T, Gandhi T.K, Seger AC, Hsieh TC, Bates DW. Adverse drug events and medication errors: detection and classification methods. Qual Saf Health Care 2004 August;13(4):306-14.

(18) Vlug AE, van der Lei J, Mosseveld BM et al. Postmarketing surveillance based on electronic patient records: the IPCI project. Methods Inf Med 1999 December;38(4-5):339-44.

(19) Field TS, Gurwitz JH, Harrold LR et al. Strategies for detecting adverse drug events among older persons in the ambulatory setting. J Am Med Inform Assoc 2004 November;11(6):492-8.

(20) Kaushal R. Using chart review to screen for medication errors and adverse drug events. Am J Health Syst Pharm 2002 December 1;59(23):2323-5.

(21) Allan EL, Barker KN. Fundamentals of medication error research. Am J Hosp Pharm 1990 March;47(3):555-71.

(22) Mitchell AS, Henry DA, Sanson-Fisher R, O'Connell DL. Patients as a direct source of information on adverse drug reactions. BMJ 1988 October 8;297(6653):891-3.

(23) Jha AK, Kuperman GJ, Teich JM et al. Identifying adverse drug events: development of a computer-based monitor and comparison with chart review and stimulated voluntary report. J Am Med Inform Assoc 1998 May;5(3):305-14.

(24) Kane-Gill SL, Kirisci L, Pathak DS. Are the Naranjo criteria reliable and valid for determination of adverse drug reactions in the intensive care unit? Ann Pharmacother 2005 November;39(11):1823-7.

(25) Arimone Y, Begaud B, Miremont-Salame G et al. Agreement of expert judgment in causality assessment of adverse drug reactions. Eur J Clin Pharmacol 2005 May;61(3):169-73.

(26) Haynes K, Hennessy S, Morales KH et al. Inter-rater Reliability of a Classification System for Hospital Adverse Drug Event Reports. Clin Pharmacol Ther 2007 August 22.

(27) Naranjo CA, Busto U, Sellers EM et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981 August;30(2):239-45.

(28) Kramer MS, Leventhal JM, Hutchinson TA, Feinstein AR. An Algorithm for the Operational Assessment of Adverse Drug Reactions. JAMA 1979;242:623-32.

(29) WHO-UMC Causality Assessment System. 2006. http://www.who.umc.org

(30) Kaushal R, Bates DW. Information technology and medication safety: what is the benefit? Qual Saf Health Care 2002 September;11(3):261-5.

(31) Chaudhry B, Wang J, Wu S et al. Systematic review: impact of health information technology on quality, efficiency, and costs of medical care. Ann Intern Med 2006 May 16;144(10):742-52.

(32) Bates DW, Leape LL, Cullen DJ et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. JAMA 1998 October 21;280(15):1311-6.

(33) Eslami S, de Keizer NF, Abu-Hanna A. The impact of computerized physician medication order entry in hospitalized patients--a systematic review. Int J Med Inform 2008 June;77(6):365-76.

(34) Wolfstadt JI, Gurwitz JH, Field TS et al. The effect of computerized physician order entry with clinical decision support on the rates of adverse drug events: a systematic review. J Gen Intern Med 2008 April;23(4):451-8.

(35) Ammenwerth E, Schnell-Inderst P, Machan C, Siebert U. The Effect of Electronic Prescribing on Medication Errors and Adverse Drug Events: A Systematic Review. J Am Med Inform Assoc 2008 September;15(5):585-600.

(36) Koppel R, Metlay JP, Cohen A et al. Role of computerized physician order entry systems in facilitating medication errors. JAMA 2005 March 9;293(10):1197-203.

(37) Han YY, Carcillo JA, Venkataraman ST et al. Unexpected increased mortality after implementation of a commercially sold computerized physician order entry system. Pediatrics 2005 December;116(6):1506-12.

(38) Kuperman GJ, Bobb A, Payne TH et al. Medication-related clinical decision support in computerized provider order entry systems: a review. J Am Med Inform Assoc 2007 January;14(1):29-40.

(39) Rommers MK, Teepe-Twiss IM, Guchelaar HJ. Preventing adverse drug events in hospital practice: an overview. Pharmacoepidemiol Drug Saf 2007 October;16(10):1129-35.

(40) Beuscart-Zephir MC, Pelayo S, Anceaux F, Meaux JJ, Degroisse M, Degoulet P. Impact of CPOE on doctor-nurse cooperation for the medication ordering and administration process. Int J Med Inform 2005 August;74(7-8):629-41.

(41) Campbell EM, Guappone KP, Sittig DF, Dykstra RH, Ash JS. Computerized Provider Order Entry Adoption: Implications for Clinical Workflow. J Gen Intern Med 2008 November 20.

(42) Pirnejad H, Niazkhani Z, van der SH, Berg M, Bal R. Impact of a computerized physician order entry system on nurse-physician collaboration in the medication process. Int J Med Inform 2008 June 2.

(43) Wu RC, Laporte A, Ungar WJ. Cost-effectiveness of an electronic medication ordering and administration system in reducing adverse drug events. J Eval Clin Pract 2007 June;13(3):440-8.

(44) Kuperman GJ, Gibson RF. Computer physician order entry: benefits, costs, and issues. Ann Intern Med 2003 July 1;139(1):31-9.

Part I Chapter 2

Reliability of the assessment of preventable adverse drug events in daily clinical practice

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Abstract

Purpose

To determine the reliability of the assessment of preventable adverse drug events (ADEs) in daily practice and to explore the impact of the assessors' professional background and the case characteristics on reliability.

Methods

We used a combination of the simplified Yale algorithm and the NCC MERP scheme to assess on the one hand the causal relationship between medication errors (MEs) and adverse events in hospitalised patients and on the other hand the severity of the clinical consequence of MEs. Five pharmacists and five physicians applied this algorithm to 30 potential MEs. After individual assessment, the pharmacists reached consensus and so did the physicians. Outcome was both MEs' severity (ordinal scale, NCC MERP categories A-I) and the occurrence of preventable harm (binary outcome, NCC MERP categories A-D vs E-I). Kappa-statistics was used to assess agreement.

Results

The overall agreement on MEs' severity was fair for the pharmacists (kappa=0.34) as well as for the physicians (kappa=0.25). Overall agreement for the ten raters was fair (kappa=0.25) as well as the agreement between both consensus outcomes (kappa=0.30).

Agreement on the occurrence of preventable harm was higher, ranging from kappa=0.36 for the physicians through kappa=0.49 for the pharmacists. Overall agreement for the ten raters was fair (kappa=0.36). The agreement between both consensus outcomes was moderate (kappa=0.47). None of the included case characteristics had a significant impact on agreement.

Conclusions

Individual assessment of preventable ADEs in real patients is difficult, possibly because of the difficult assessment of contextual information. Best approach seems to be a consensus method, including both pharmacists and physicians.

Introduction

Drugs have undoubtedly contributed to a better disease control. However, besides their obvious benefits they have untoward harmful effects, i.e. adverse drug events (ADEs). These events can occur as either adverse drug reactions (non-preventable) or as harm due to medication errors (MEs) (preventable).[1] Historically, the focus has been on 'idiosyncratic' adverse drug reactions (ADRs) especially since the thalidomide disaster in the 1960s. Lately, the focus has been shifting towards preventable ADEs.[2] Minimising this type of events makes health care safer, for which various risk reduction strategies (e.g. computerised physician order entry) have been developed. However, to critically assess the strategies' impact on patient safety, reliable instruments are needed to identify preventable ADEs. These instruments should not only be applicable for scientific purposes but also in daily clinical practice.

Various instruments have been developed and are being used to assess in a systematic way the causality between a drug and an adverse event.[3-7] The structure of these instruments varies from sets of questions to complex algorithms. Their focus usually is the assessment of ADRs (non-preventable) and not specifically the assessment of preventable ADEs. Specific instruments for assessing the drug causality of preventable ADEs are to our knowledge not available. Nevertheless, the underlying principle of assessing ADRs and preventable ADEs is the same. Therefore the aforementioned instruments can in our view be applied to preventable ADEs as well.

If there is a causal relationship, the severity of the consequence of the error can be classified. For classification of the severity of an error the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) index [8] is widely used. This index was recently found to be reliable based on the substantial agreement between the assessors.[9] In this study the assessment was based on centrally extracted data pertaining to the occurrence of a specific event and presented in a standardised format to experienced assessors who were mainly pharmacists. This leaves open the question about the reliability and the generalisability to everyday practice, in which MEs and related ADEs are not assessed by specialised pharmacists on extracted data, but have to be made based on data from medical charts with a variety of clinical information and by professionals, who are not specifically trained as assessors. Nevertheless, it is important to know this reliability. Only if both physicians and pharmacists agree on the presence or absence of preventable ADEs, useful strategies for reduction of these events in daily practice can be developed and implemented in a successful way. And only on this condition, a positive effect of these strategies can be expected.

The aim of this study is to determine the reliability of the assessment of preventable ADEs in daily practice (i.e. assessment by practicing physicians and pharmacists

using complete clinical information), and to explore the impact of the assessors' professional background and the case characteristics on reliability.

Methods

Setting

This study was part of a larger study on the effect of a computerised Physician Order Entry system on Medication Safety and costs (the POEMS study), which collected data in three internal medicine wards (two general internal medicine wards and one gastroenterology/rheumatology ward) of the 1300 bed University Medical Center Groningen and in two internal medicine wards (one geriatric and one general internal medicine ward) of the 600 bed teaching hospital 'TweeSteden' in Tilburg, the Netherlands.

A waiver of the Medical Ethical Committee was obtained for this study, as the study fell within the boundaries of normal hospital routine of quality improvement and assurance. However, to protect patient privacy, patients were informed of the study and could object to inclusion of the study.

Study population & data collection

In the POEMS study, patients admitted to the study wards were included from July 2005 through November 2005. Patients received a letter with information about the study and they could object to inclusion. During daily ward visits, data on patients' characteristics, diseases, medication, laboratory values and adverse events were prospectively extracted by chart review. Two research pharmacists initially reviewed the medication and identified potential prescribing and transcribing errors according to the classification scheme for medication errors of the Netherlands Association of Hospital Pharmacists.[10] Prescribing errors were defined as errors in the process of prescribing drugs and were subdivided into administrative (e.g. errors on readability, drug name or route of administration), dosing (e.g. errors on dosage, frequency or length of therapy) and therapeutic errors (e.g. interactions, contra-indications or duplicate therapy). Transcribing errors were defined as errors in the process of interpreting, verifying and transcribing of medication orders (MOs). For the current study, 30 patients were randomly selected, for whom in the initial medication review at least one potential medication error (ME) was detected by one of the two research pharmacists.

Assessment tool

To standardise the assessment procedure for POEMS, we combined the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) scheme with the simplified Yale algorithm[3] (**Figure 1**). The NCC MERP scheme cat-

egorises MEs into nine categories (A through I) based on severity of related patient outcomes; our first primary outcome (**Table 1**). Categories A through D are associated with the absence of a preventable ADE, and Categories E through I are associated with the presence of a preventable ADE. These collapsed categories, A-D and E-I, form our secondary outcome. The Yale algorithm assesses the causality of the association between a drug and an adverse event.[3] We adopted the first three items of the Yale algorithm (knowledge about the relation between this drug and the event, influence of other clinical conditions and the time relation between drug and event). The causal relationship could be assessed as unlikely (score < 0), possible (score ≥ 0 and ≤ 3) and probable (score = 4). Combining these algorithms, an event was defined as a preventable adverse drug event when it was possible or probable related to an ME.

Table 1: NCC MERP Categories

Category	Content
A	Circumstances or events that have the capacity to cause error
B	An error occurred but the error did not reach the patient
C	An error occurred that reached the patient but did not cause patient harm
D	An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm
E	An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention
F	An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalisation
G	An error occurred that may have contributed to or resulted in permanent patient harm
H	An error occurred that required intervention necessary to sustain life
I	An error occurred that may have contributed to or resulted in the patient's death

Figure 1 (on the next page): Combinaton of the NCC MERP scheme and the simplified version of the Yale algorithm.

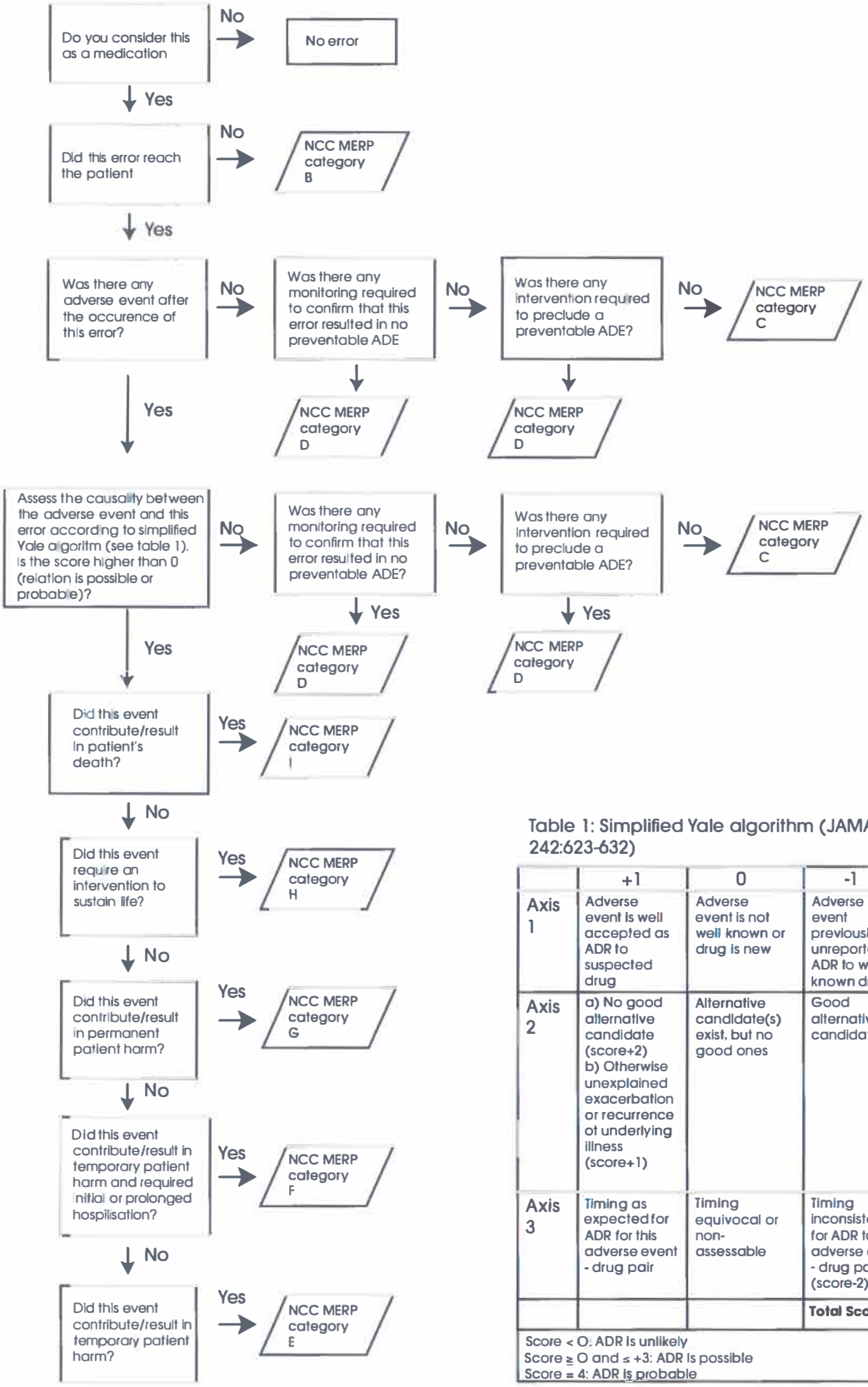


Table 1: Simplified Yale algorithm (JAMA 1979; 242:623-632)

	+1	0	-1	Score
Axis 1	Adverse event is well accepted as ADR to suspected drug	Adverse event is not well known or drug is new	Adverse event previously unreported as ADR to well known drug	
Axis 2	a) No good alternative candidate (score+2) b) Otherwise unexplained exacerbation or recurrence of underlying illness (score+1)	Alternative candidate(s) exist, but no good ones	Good alternative candidate	
Axis 3	Timing as expected for ADR for this adverse event - drug pair	Timing equivocal or non-assessable	Timing inconsistent for ADR for this adverse event - drug pair (score-2)	
			Total Score	

Score < 0: ADR is unlikely
Score ≥ 0 and ≤ +3: ADR is possible
Score ≥ 4: ADR is probable

Assessment procedure

The reliability of the assessment tool (combination of the NCC MERP scheme and the simplified Yale algorithm) was tested using the following procedure. All patients' clinical information, including the identified potential MEs in the initial medication review by one of the two research pharmacists, was given to two panels. The first panel consisted of five pharmacists of whom two were specialised as hospital pharmacists. Two of them were connected to the TweeSteden hospital, the others to the University Medical Center Groningen. Three pharmacists had experience in clinical practice for more than 5 years. The other two were involved in the POEMS study as members of the research team. The second panel consisted of five physicians who were all specialised in internal medicine. Three of them were geriatricians and four of them were registered as clinical pharmacologists. One of the physicians was connected to the TweeSteden hospital, two to the University Medical Center Groningen and two to other Dutch hospitals (in Utrecht and Helmond). All physicians had experience in clinical practice for more than 5 years.
Before assessing the thirty cases, the raters were individually instructed how to use the assessment tool by one of the two researchers.
These panels performed a detailed medication review. The clinical information available to these assessors consisted of patients' characteristics, diseases, all medication used (home- and hospital-initiated), adverse events, laboratory data and discharge letters. The panel members assessed individually the same potential MEs. After individual assessment of all 30 cases, the five pharmacists (panel 1) reached consensus on all cases in one plenary meeting and so did the five physicians (panel 2) in their own plenary meeting after individual assessment.

Outcome variable

Two outcome variables were defined; (a) the severity of an ME (NCC MERP categories A through I) and (b) a dichotomised version of this severity score, namely presence (NCC MERP categories E through I) or absence (NCC MERP categories A through D) of a preventable ADE as assessed by the panel.

Determinants

The assessors' professional background (pharmacist versus physician) was studied as determinant for agreement. The case characteristics included as determinants were patients' age (≥ 75 years versus < 75 years), patients' length of hospital stay on the study ward (≥ 20 days versus < 20 days), number of medication orders per case (≥ 15 medication orders versus < 15 medication orders), the medical ward's specialism to which patients were admitted (geriatrics versus internal medicine including gastroenterology/rheumatology and general internal medicine patients), and the type of ME (dosing errors versus therapeutic errors). Cut-off points were based on the mean observed results.

We chose as determinants those characteristics of which we thought that they could have an influence on agreement.

Data analysis

Agreement was calculated by using kappa statistics. For this calculation, the software program, AGREE® version 7 (ProGAMMA™, the Netherlands) was used.
Kappa values less than 0.20 were considered as poor agreement, between 0.21 and 0.40 as fair agreement, between 0.41 and 0.60 as moderate agreement, between 0.61 and 0.80 as good agreement and between 0.81 and 1.00 as very good agreement.[11]
Agreement was calculated for both outcomes; the severity of medication errors (expressed as an ordinal scale from NCC MERP index categories A - I) as well as the presence/absence of a preventable ADE expressed as a binary outcome (absence; NCC MERP index categories A through D, versus presence; categories E - I).
The impact of assessors' professional background on agreement was assessed by calculating the overall agreement for all 30 cases within the total group of assessors, within the group of pharmacists and within the group of physicians. To determine the impact of reaching consensus within both expert panels on reliability, agreement between both consensus outcomes (pharmacists vs. physicians) was calculated.
To explore the impact of case characteristics on agreement, the cases were divided into groups with specific case characteristics. Agreement within the total group of assessors was calculated for these groups.
The significance of the differences between kappa values was determined, using AGREE®, version 7. A p-value of less than 0.05 was considered statistically significant.
The selected 30 cases had a power of 80% to detect a kappa difference of 0.25 (α =0.05). This was based on an initial estimation of the distribution of ME's severity (NCC MERP).

Results

Study population

The mean age of the study population was 77 ± 15 years. They received 17 ± 9 medication orders during their hospital stays on the study wards, which lasted on average 20 ± 9 days. Nineteen patients were admitted to the geriatric ward, seven patients to the general internal medicine ward and four patients to the gastroenterology/rheumatology ward. (Table 2)
Potential MEs included fourteen dosing errors, eleven therapeutic errors, five transcribing errors and no administrative errors.

Table 2: Patient characteristics of study population (n = 30)

Female (n,%)	13 (43%)
Age (years)	77 ± 15
Length of stay on ward (days)	20 ± 9
Medication orders per patient (mean ± SD)	17 ± 9
Geriatric patients (n = 19) Primary discharge diagnoses	Delirium (4), mobility problems (4), mental disorders (3), cancer (2), pneumonia (2), hyponatremia based on medication use*, myocardial infarction, urinary tract infection, pulmonary embolism
General internal medicine (n = 7) Primary discharge diagnoses	Cancer (2), sepsis, deregulated diabetes mellitus, gastroenteritis, cellulites, ileus
Gastroenterology/rheumatology ward (n = 4) Primary discharge diagnoses	Cancer (2), cholangitis, cholestasis

* This adverse drug event was the reason for admission and did not occur during admission

Agreement between assessors

The agreement between the 10 raters was fair for both outcomes: the severity of MEs ($\kappa = 0.25$) as well as the presence/absence of a preventable ADE ($\kappa = 0.36$). The agreement on the severity of MEs was fair within the group of pharmacists ($\kappa = 0.34$) and within the group of physicians ($\kappa = 0.25$) (**Table 3**). The agreement between the consensus outcomes was also fair ($\kappa = 0.30$).

The agreement on the presence/absence of a preventable ADE was slightly higher; moderate for the pharmacists ($\kappa = 0.49$) and fair for the physicians ($\kappa = 0.36$) (**Table 3**). The agreement between both consensus outcomes was moderate ($\kappa = 0.47$).

Table 3: Agreement between assessors

Raters	Severity of MEs Kappa (95% CI)	Presence/absence of a preventable ADE Kappa (95% CI)
Agreement for individual assessment		
within total group of assessors n=10)	0.25 (0.18 - 0.32)[#]	0.36 (0.23 - 0.49)[#]
within group of pharmacists (n=5)	0.34 (0.21 - 0.47)[*]	0.49 (0.29 - 0.68)[†]
within group of physicians (n=5)	0.25 (0.14 - 0.35)[*]	0.36 (0.23 - 0.49)[†]
Consensus		
Between pharm. and phys.(n = 2)	0.30 (0.09 - 0.50)[§]	0.47 (0.15 - 0.78)[§]

No significant difference between:

[#] the severity of MEs and the presence/absence of a preventable ADE: p = 0.73

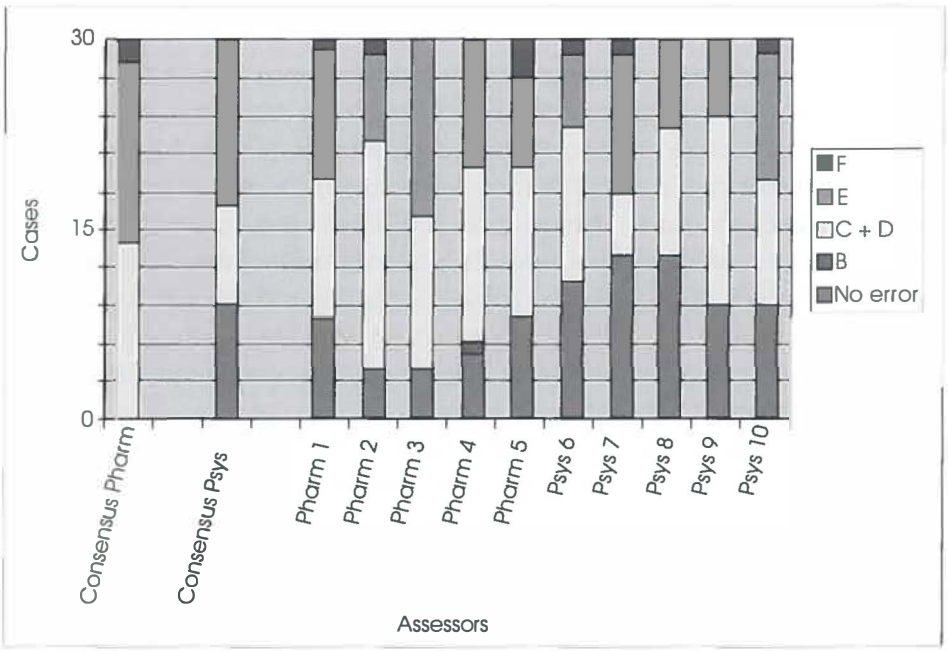
[*] pharmacists and physicians: p = 0.28

[†] pharmacists and physicians: p = 0.30

[§] the severity of MEs and the presence/absence of a preventable ADE: p = 0.74

For pharmacists, the agreement on both the severity of MEs and presence/absence of a preventable ADE seemed to be higher than for the physicians. However these differences were not significant. In the consensus procedure, the physicians assessed nine potential MEs as no error while the pharmacists considered all cases as an error (**Figure 2**). Pharmacists as well as physicians did not assess medication errors more severe than classification F; i.e. errors leading to prolonged hospitalisation. Medication errors in these 30 cases were not assessed to be associated with permanent patient harm, needing interventions to sustain life, or with patient's death.

Figure 2: Outcomes of the ten assessors



Pharm = pharmacist

Phys = physician

Impact of case characteristics on agreement

Of the different types of medication errors, only dosing errors and therapeutic errors were included as determinant because of the small number of transcribing errors (n=5). None of the included case characteristics had a significant impact on agreement (data not shown).

Cases

The cases are described in more detail in the **APPENDIX,** both for cases with agreement **(table 4)** and for cases with disagreement **(table 5).**

Discussion

Only in two cases the level of agreement between raters was higher than fair, i.e. the agreement on the presence of a preventable ADE within the pharmacists panel, and between the two consensus assessments. As is already known from studies into the assessment of ADRs (non-preventable), it is difficult to reach good agreement between raters whether there is a standardised procedure or not.[12-14] Our findings underline it is the same for assessing preventable ADEs and their severity from medical charts in everyday practice. This is in line with the recently published study of Haynes *et al.*[15] but surprisingly is in contrast with high inter rater agreement found by Forrey *et al.*[9] and Snyder *et al.*[16] So, why do some studies find such poor agreement while others do not?

First, the level of detail of case information given to the assessors differs. Instead of extracted information associated with an adverse drug event or medication error only [9,16], we used an overview of all available clinical information during hospital admission. Yet, this overview reflects the reality of clinical situations, in which individual patients have various diseases, use many different medications and experience several symptoms that can be adverse drug events or are caused by the normal disease process.

Secondly, in our study we made use of professionals, not specialised in assessing ADEs. This is not in line with most other studies, where judgements were made by specialised assessors. For example, in the study of Forrey *et al.*[9] the health care professionals were regular MEDMARX users and the researchers could not exclude that they were more experienced in assessing medication errors. However, when implementing strategies to improve medication safety in everyday practice, specialised assessors are not always available in sufficient numbers in individual hospitals. Moreover even such specialised assessors have been shown to disagree significantly possibly because of variations in subjective weighing of causality arguments.[13,14] This affects mainly arguments that are not factual (i.e. other risk factors or comorbidities which could have been the actual reason for the event).

Thirdly, a learning curve could explain higher levels of agreement. In the study by Snyder *et al.*[16] each case was assessed, then classified after discussion by the individual raters before moving to the next case. This is in contrast to both the study of Haynes et al.[15] (in which raters individually classified only without discussion) and our study, in which only after all cases were classified individually, consensus was reached in a subsequent meeting. We chose for this method, because our goal was to determine agreement between individual assessors prior to consensus building in order to evaluate the 'average' healthcare professional opinion on preventable ADEs. In our study, discussion could not have influenced the individual

ratings in contrast to the approach by Snyder et al.[16] that could have resulted in a learning curve and finally higher agreement.

A potential barrier for implementing strategies to increase medication safety is the rather low agreement between pharmacists and physicians when assessing preventable ADEs. The physicians in our study considered nearly a third of all potential MEs not to be a real error. In contrast, the pharmacists rated all potential MEs as real errors. We can not exclude that the difference in clinical experience between the physicians and the pharmacists had an impact on this result. Besides, physicians will probably assess medication safety issues from another perspective than pharmacists do, because of differences in education, specialisation and experiences. Furthermore, it could be hypothesised that physicians look at the patient and his disease first and will then consider the relevance of an error, while pharmacists in their daily routine are focused on the medication process (how this could be improved) and on pharmacological aspects from a more drug related view. This may have influenced the group process and outcome of the classification. Still, the different professional groups were in moderate agreement on the presence/absence of a preventable ADE after the consensus procedure. However, agreement within the group of physicians remained fair only. Overall we may conclude that the impact of profession is not unambiguously clear neither in our study nor in that of Dean and Barber [17], who also found that reliability was not affected by profession (comparing pharmacists, physicians and nurses).

A remarkable finding is that in the consensus ratings of the pharmacists there were no 'no error' ratings while each pharmacist individually had rated some MEs as 'no error'. A possible explanation could be that one of the raters was leading in the consensus meeting. Therefore, we determined the agreement between the individual raters and the consensus outcomes for both pharmacists and physicians (data not shown). Based on these results, we draw the conclusion that none of the pharmacists was particularly dominant. The same applies to the physicians. Unfortunately, we are not able to further explain the reason for the difference between individual and consensus ratings than that this may have been a chance occurrence.

Our findings did not indicate an effect of the studied case characteristics, but can also not completely rule out they did not. Decision making by the individual assessors does not seem to be influenced by the case characteristics investigated. The results may however not extend to other specialities than internal medicine as only patients from these departments were included in this study. Specific population characteristics, e.g. children, may have a different effect on agreement. However, internal medicine patients use in general relatively many drugs and are therefore a relevant population for evaluating the reliability of assessing medication safety.

This study shows that there is only fair agreement on the assessment of an adverse event being actually preventable harm. Our conclusion is the same as Haynes' *et al.*[15]; it is still a challenge to assess ADEs in a reliable way. As long as the reliability is low, it will be difficult to determine the absolute number of preventable ADEs. This problem has to be addressed when developing useful strategies to improve medication safety in everyday practice. Although consensus methods have their limitations, the best practical solution seems to be the consensus method including both pharmacists and physicians because it will increase the acceptability in the field which is necessary when implementing change.

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Conflict of interests

None declared.

References

(1) *Morimoto T, Gandhi TK, Seger AC, Hsieh TC, Bates DW. Adverse drug events and medication errors: detection and classification methods. Qual Saf Health Care 2004 Aug;13(4):306-14.*

(2) *Institute of Medicine. To Err is Human: Building a Safer Health System (1999). http://www.iom.edu/, last accessed October, 2007.*

(3) *Kramer MS, Leventhal JM, Hutchinson TA, Feinstein AR. An Algorithm for the Operational Assessment of Adverse Drug Reactions. JAMA 1979;242:623-32.*

(4) *Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt MD. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981 Aug;30(2):239-45.*

(5) *Jones JK. Adverse drug reactions in the community health setting: approaches to recognizing, counseling, and reporting. Fam Community Health 1982 Aug;5(2):58-67.*

(6) *Karch FE, Lasagna L. Toward the operational identification of adverse drug reactions. Clin Pharmacol Ther 1977 Mar;21(3):247-54.*

(7) *WHO-UMC. Causality Assessment of Suspected Adverse Reactions. http://www.who-umc.org/, last accessed October, 2007.*

(8) *National Coordinating Council For Medication Error Reporting and Prevention (NCC-MERP). NCC MERP Index for Categorizing Medication Errors. http://www.nccmerp.org/, last accessed October, 2007.*

(9) *Forrey RA, Pedersen CA, Schneider PJ. Interrater agreement with a standard scheme for classifying medication errors. Am J Health Syst Pharm 2007 Jan 15;64(2):175-81.*

(10) *Bemt van den PMLA, Egberts ACG. Drug-related problems: definitions and classifications. EJHP 2006;12((suppl.)):10-2.*

(11) *Altman DG. Practical statistics for medical research. London: Chapman & Hall, 1991.*

(12) *Koch-Weser J, Sellers EM, Zacest R. The ambiguity of adverse drug reactions. Eur J Clin Pharmacol 1977 Jan 3;11(2):75-8.*

(13) *Arimone Y, Begaud B, Miremont-Salame G, Fourrier-Reglat A, Moore N, Molimard M, Haramburu F. Agreement of expert judgment in causality assessment of adverse drug reactions. Eur J Clin Pharmacol 2005 May;61(3):169-73.*

(14) *Arimone Y, Miremont-Salame G, Haramburu F, Molimard M, Moore N, Fourrier-Reglat A, Bégaud B. Inter-expert agreement of seven criteria in causality assessment of adverse drug reactions. Br J Clin Pharmacol 2007 Oct;64(4):482-8.*

(15) *Haynes K, Hennessy S, Morales KH, Gibson GA, Barnhart C, Jaipaul CK, Linkin DR. Inter-rater Reliability of a Classification System for Hospital Adverse Drug Event Reports. Clin Pharmacol Ther 2008 Mar; 83(3): 485 – 488.*

(16) *Snyder RA, Abarca J, Meza JL, Rothschild JM, Rizos A, Bates DW. Reliability evaluation of the adapted National Coordinating Council Medication Error Reporting and Prevention (NCC MERP) index. Pharmacoepidemiol Drug Saf 2007 Sep;16(9):1006-13.*

(17) *Dean BS, Barber ND. A validated, reliable method of scoring the severity of medication errors. Am J Health Syst Pharm 1999 Jan 1;56(1):57-62.*

Appendix

Table 4: Cases with agreement

16 cases with agreement (between both consensus outcomes)		Type of ME
Agreement on the occurrence of a preventable ADE (n=10)	Hypotension → Overdose of Perindopril	Dosing
	Rash → A prescription of Flucloxacillin for a patient with a known allergy for this drug	Therapeutic
	Unrest → Stop of administration of Strumazol® (antithyroid drug) because of a transcribing error	Transcribing
	Agitation → Prescription of high dose of oxycontin® (opioid) at once instead of increasing gradually	Dosing
	Hypoglycemia → Gliclazide administered on wrong moment because of a transcribing error	Transcribing
	Bleeding nose → Continuation of Clopidogrel instead of stopping	Therapeutic
	Edema → Interaction between Clarithromycin and Nifedipine	Therapeutic
	Dizziness → Overdose of Ipratropium	Dosing
	Hyperkalemia → Duplicate therapy of Perindopril and Irbesartan	Therapeutic
	Decrease of INR → Stop of administration of Acenocoumarol because of a transcribing error	Transcribing
Agreement on the occurrence of an ME without a preventable ADE (n=6)	Pravastatin 20 mg → Prescribed to administer it in the morning instead of in the evening	Dosing
	Albumin 100 cc → No indication for this drug	Therapeutic
	Isosorbide mononitrate 50 mg → Prescribed twice a day instead of once a day (nitrate free interval is required because of nitrate tolerance)	Dosing
	Nitrofurantoin 100 mg→ wrong scheme of administration: 100 mg twice a day instead of 50 mg four times a day (mistaken for the capsule with extended release)	Dosing
	Nitrofurantoin 100 mg → Prophylaxis: prescribed to administer in the morning instead of in the evening	Dosing
	Rifampicin 600 mg → Interacts with midazolam (may decrease the level of midazolam)	Therapeutic

Table 5: Cases with disagreement

14 cases with disagreement (between both consensus outcomes)		Type of ME
Agreement on the occurrence of an ME, disagreement on the occurrence of a preventable ADE (n = 5)	*Preventable harm, only according to pharmacists:*	
	Clostridium difficile infection → Overdose of ceftazidime	Dosing
	Decrease of INR → Stop of administration of Acenocoumarol because of a transcribing error	Transcribing
	Preventable harm, only according to physicians:	
	Haematuria, diarrhea, vomiting → Overdose of cotrimoxazole prescribed for a patient with renal impairment	Dosing
	Rectal prolapse → No administration of microlax®, an enema (a laxative), because of an omission of the nurses to transcribe this drug on the administration chart.	Transcribing
	Increase of alkaline phosphatase → Overdose of acetaminophen	Dosing
Disagreement on the occurrence of an ME (n=9)	*MEs only according to pharmacists:*	
	Ferrous fumarate 200 mg once a day: an underdose.	Dosing
	Prescriptions of both aspirin and dexamethasone. No prescription of a proton pump inhibitor.	Therapeutic
	Acenocoumarol prescribed to a patient with a history of duodenal ulcer. No prescription of a proton pump inhibitor.	Therapeutic
	Duplicate therapy of lactulose and magnesium hydroxide (both laxatives).	Therapeutic
	Hydroxocobalamin 1 mg / 3months: underdose	Dosing
	Nitrofurantoin prescribed to a patient with a creatinine clearance probably of 50 mL/minute. Patient's weight was not known.	Therapeutic
	Various switches of antibiotics: indication not clear.	Therapeutic
	Domperidone 60 mg 3 times a day (suppository): an overdose.	Dosing
	Allopurinol 300 mg once a day prescribed to a patient with a creatinine clearance lower than 60 mL/minute: an overdose.	Dosing

Chapter 3

Medication errors: the impact of prescribing and transcribing errors on preventable harm in hospitalised patients

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Abstract

Background

Medication errors (MEs) affect patient safety to a significant extent. Because these errors can lead to preventable adverse drug events (pADEs), it is important to know what type of MEs is the most prevalent cause of these pADEs. This study determined the impact of the various types of prescribing (administrative, dosing and therapeutic) and transcribing errors on pADEs in hospitalised patients.

Methods

During a 5-month period, data of patients admitted to a total of five internal medicine wards of one university and one teaching hospital in the Netherlands were prospectively collected by chart review. In each hospital, MEs were detected and classified by the same pharmacist, using the classification scheme for MEs developed by the Netherlands Association of Hospital Pharmacists. The primary outcome measure was the prevalence of pADEs during hospital stay. In consensus meetings, five pharmacists assessed the causal relationship between MEs and pADEs. The association between type of ME and pADEs was determined by a multivariate regression analysis taking into account potential confounders.

Results

The study included 592 hospital admissions with 7286 medication orders (MOs), of which 60% contained at least one prescribing or transcribing error. 1.4% of all MOs led to pADEs, concerning 14.8% of all admitted patients. The total number of pADEs was 103 of which 92 consisted of temporary harm, eight of prolongation of hospital admission, two were life-threatening and one was fatal. Therapeutic errors were most strongly associated with pADEs (odds ratio (OR), 1.98; 95% confidence interval (CI), 1.53 – 2.56).

Conclusions

Although many prescribing and transcribing errors occur in the process of medication use of hospitalised patients, a minority lead to pADEs. In particular, therapeutic errors are the cause of these pADEs and are therefore clinically relevant. Intervention and prevention programmes should primarily focus on this type of medication error.

Introduction

Improving patient safety is high on the agenda in health care since in 1999 the Institute of Medicine published its report "To Err is Human", which highlighted the magnitude of the problem of patients being harmed during medical care.[1] It showed that as many as 98,000 people die each year from medical errors in hospitals. A large proportion of these errors concern medication errors at different stages of the medication use process, including prescribing, transcribing, dispensing and administering of drugs,[2] with prescribing errors being the most common.[3-5] The frequency of the different types of errors varies across settings, but the differences may also be explained by the differences in definitions of medication errors and differences in the methodology of determining medication errors.

Next to defining the prevalence of these different types of medication errors, some studies have determined the potential harm these medication errors could cause without determining whether that harm actually occurred.[5,6] Therefore only an estimation of the clinical impact of medication errors can be made as occurrence of real harm related to medication errors is only inferred. Increasingly, prospective cohort and observational studies screen for injuries caused by medication, i.e. adverse drug events (ADEs).[3,4,7-11] These studies have also assessed whether an ADE that occurred was associated with a medication error and therefore was considered to be preventable. About 26% to 42% of the ADEs were preventable and these preventable adverse drug events (pADEs) seemed to be mainly caused by prescribing and transcribing errors.[3,4,8,11]

To minimise pADEs, it is important to know the relation between the subtypes of prescribing and transcribing errors and the risk of pADEs. Unfortunately, little is known about this relation. Yet, such information would provide important clues as to which type of errors cause most harm and should therefore be the primary focus for intervention and prevention programmes. Therefore, we performed a study to investigate the impact of the various types of prescribing and transcribing errors on pADEs in hospitalised patients.

Methods

Setting, design and patients

This study is conducted in the framework of a study on the effect of a computerised Physician Order Entry system on Medication Safety and associated costs (POEMS study). The study was performed in three medical wards of the 1300 bed University Medical Center in Groningen (two general internal medicine wards and one gastroenterology/rheumatology ward) and in two medical wards (one geriatric and one general internal medicine ward) of the 600 bed teaching hospital 'TweeSteden' in Tilburg and Waalwijk, the Netherlands. In these medical wards, the process of medication ordering and administration consisted of a hand-written system: physicians prescribe medication orders on charts and nurses transcribe these medication orders on administration charts.

The occurrence of prescribing and transcribing errors and related harm was determined in patients hospitalised on these five medical wards using a prospective cohort design.

During a 5-month period, from July 2005 through November 2005, all patients admitted for more than 24 hours to the study wards were included. Patients received a letter with information about the study, and they could object to inclusion.

Data collection

During daily ward visits, the investigators collected data on patients' characteristics (sex, age, length and weight), diseases (reasons for admission and diagnoses), medication (medication orders during hospital stay) and adverse events (any untoward medical occurrences during stay) which consisted of newly upcoming symptoms or increasing of consisted symptoms. These data were prospectively extracted from the medical records, the medication order and administration charts. When the investigators noticed a potentially life threatening error related to a medication order during the process of data collection, they intervened in the prescribing process for ethical reasons. Such errors were not excluded from this study.

Classification of prescribing and transcribing errors

Medication errors were categorised according to the classification scheme for medication errors developed by the Netherlands Association of Hospital Pharmacists.[12] In this scheme a distinction is made between prescribing, transcribing, dispensing, administering and 'across setting' errors. In this study, only prescribing and transcribing errors were recorded. Prescribing errors are subdivided into administrative errors (errors on readability, patient data, ward and prescriber data, drug

name, dosage form and route of administration), dosing errors (errors on strength, frequency, dosage, length of therapy and directions for use) and therapeutic errors (interactions, contra-indications, incorrect monotherapy, duplicate therapy and errors on therapeutic drug monitoring or laboratory monitoring). Transcribing errors were classified as errors in the process of interpreting, verifying and transcribing of medication orders.
Inappropriate drug choices were not actively assessed and were only taken into account when these were obvious.

Classification of severity of errors

All medication errors were classified according to severity of the consequence of the error using the scheme of the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP).[13] The severity of the consequence of the medication errors could range from a medication error that did not reach the patient (B) up to a medication error that reached the patient and led to the death (I). In the NCC MERP classification, category A is meant for situations that can lead to a medication error. In this study this category is not used. This classification is illustrated in **table 1**.

Table 1: Frequency of errors per severity category

	No pADEs			pADEs				
NCCMERP category*	B	C	D	E	F	G	H	I
Prescribing								
Administrative (n=2522)	**2516** (99.8%)	**6** (0.2%)	-	-	-	-	-	-
Dosing (n=1658)	**1396** (84.2%)	**220** (13.3%)	**8** (0.5%)	**30** (1.8%)	**1** (0.1%)	-	**2** (0.1%)	**1** (0.1%)
Therapeutic (n=340)	**25** (7.4%)	**255** (75%)	**4** (1.2%)	**50** (14.7%)	**6** (1.8%)	-	-	-
Transcribing (n=1205)	**1020** (84.6%)	**167** (13.9%)	**5** (0.4%)	**12** (1.0%)	**1** (0.1%)	-	-	-
Total (n=5725)	**4957** (86.6%)	**648** (11.3%)	**17** (0.3%)	**92** (1.6%)	**8** (0.1%)	-	**2** (0.0%)	**1** (0.0%)

*NCC MERP Index for categorising medication errors:

B = An error occurred but the error did not reach the patient

C = An error occurred that reached the patient but did not cause patient harm

D = An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm

E = An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention

F = An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalisation

G = An error occurred that may have contributed to or resulted in permanent patient harm

H = An error occurred that required intervention necessary to sustain life

I = An error occurred that may have contributed to or resulted in the patient's death

Causality assessment

For all medication errors made while a patient was admitted, all adverse events that were extracted from the charts were assessed for a causal relationship. The relationship between a medication error and an adverse event only was assessed. In other words, we did not assess the relationship between drugs and adverse

events (including non preventable ADEs). This causality assessment was carried out by five pharmacists. In aid of that assessment an algorithm was developed, based on both the NCC MERP scheme and the Yale algorithm, an algorithm for the causality assessment between a drug and an event.[14] The first three items of the Yale algorithm were used; determination whether the event has been widely known to occur as a consequence of the drug's administration, whether there might be underlying clinical conditions which are responsible for the event, and whether the timing of the event is as expected in case of an ADE.
After individual assessment by the pharmacists, four meetings took place, where consensus was reached for all cases on both causality and severity. Because we expected a priori that the reliability between the individual pharmacists would be low [15,16], we made use of this consensus method. Other studies into medication safety applied a consensus procedure as well.[6,17,18] Although this method has its limitations too, such as dominant raters having an unproportionally large influence on outcome assessments, it seems to be the best practical solution.

Outcome

The measure of outcome was the prevalence of preventable adverse drug events (pADEs). A pADE was defined as an ADE that occurred due to a medication error and where the causality assessment procedure indicated that there was at least a possible relationship between ADE and medication error. In this paper, the term pADE is similar to preventable harm.

Determinants

The different types of prescribing and transcribing errors as determinants for pADEs were studied. Administrative errors were not taken into account in the analysis because there were no pADEs related to this type of error. Patients' age, patients' sex, number of errors related to one patient, number of medication orders related to one patient and drug groups, associated with high risk on preventable harm were considered as potential confounders. Relevant drug groups were selected from both the literature,[19] and the associations with pADEs in our own data (percentage of pADEs per prescribed drug group). These were antidiabetics, anticoagulants, drugs for anaemia, corticosteroids, antibiotics for systemic use, anti-inflammatory drugs, analgesics, antiepileptics, psycholeptics and drugs for gout.

Data analysis

All data were processed with MS Access 2003. SPSS version 12 and the SAS statistical package version 9.1 were used for analysis. The association between type of medication error and pADEs was determined by logistic regression analysis with the patient as unit of analysis. Patients were included only when a medication

error had occurred. Potential confounders were taken into account in a univariate analysis. Potential confounders from the univariate analysis ($p<0.05$) were included into a multivariate logistic regression model.

Results

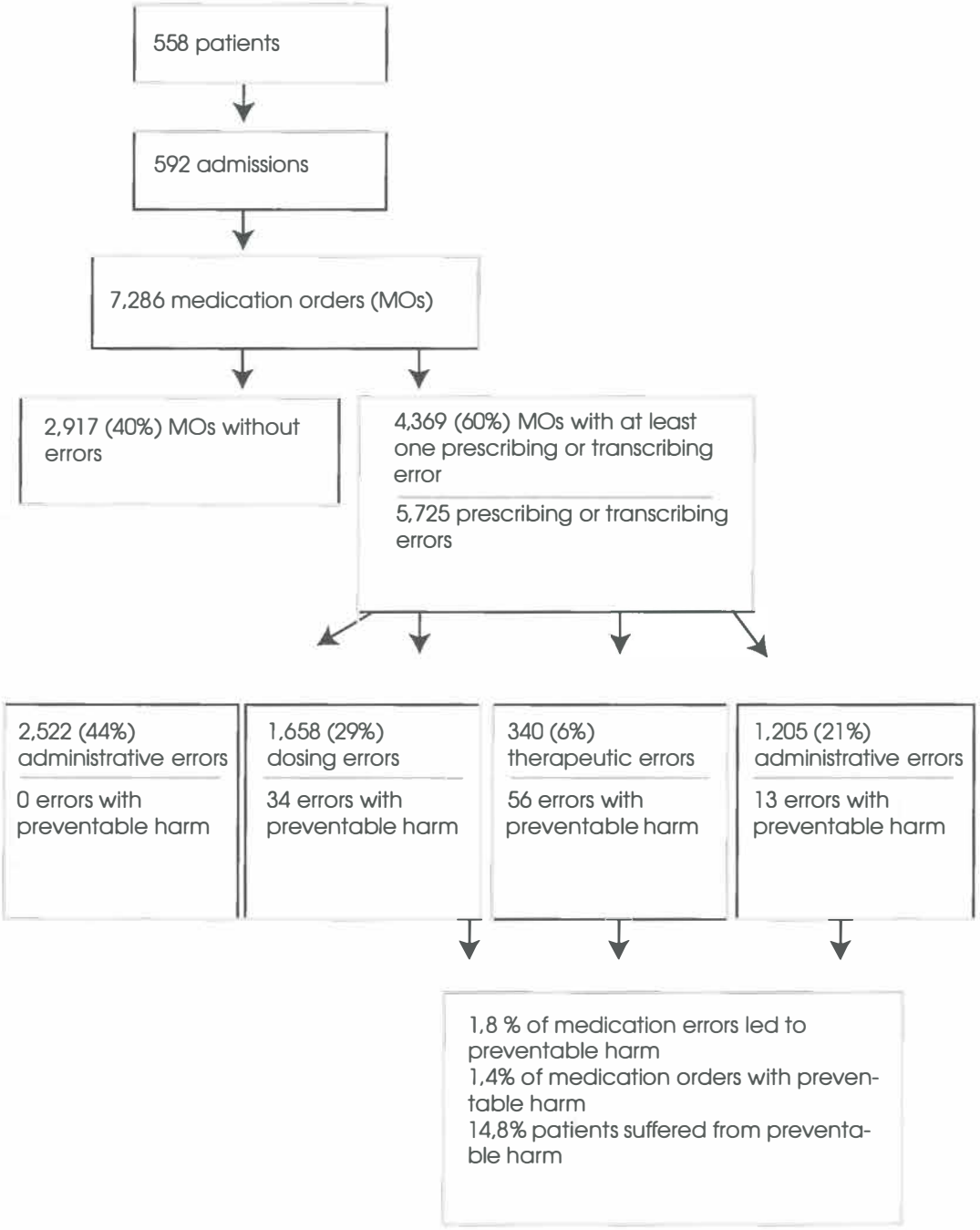
During the 5-month period of data collection, 558 patients with 592 hospital admissions were included in this study (28 patients were re-admitted once and three patients were re-admitted twice). Four patients did not provide consent and were excluded from the study. **Table 2** summarises the characteristics of all study patients.

Table 2: Characteristics of all study patients

Characteristic	Admissions (n = 592)
Female (n,%)	324 (55%)
Age (years)	65.5 ± 19.2
Length of hospital stay on study wards (days)	14.6 ± 12.5
Medication orders per hospital stay (mean ± SD)	12.3 ± 7.8
Patients admitted to:	
gastroenterology/rheumatology (n,%)	188 (31.8%)
internal medicine (n,%)	251 (42.4%)
geriatrics (n,%)	153 (25.8%)

A total of 7286 medication orders were written, of which 4369 (60%) contained at least one prescribing or transcribing error. A total number of 5725 prescribing or transcribing errors were identified, of which 103 (1.8%) resulted in preventable harm **(Figure 1)**. In nine cases, the study investigators intervened to preclude unacceptable patient harm: four dosing errors and five transcribing errors. These errors were classified as D; errors that required an intervention to preclude harm.

Figure 1: frequency of patients, medication orders and medication errors



*percentage of total number of medication errors

Table 1 shows the frequency of each type of error classified within a severity category. The most commonly identified type of medication error was an administrative error, but this type caused no pADEs. **(Figure 1 and Table 1)** In contrast, 56 (16%) of a total of 340 therapeutic errors led to a pADEs. Examples of prescribing and transcribing errors related to pADEs are given in **table 3.**

Table 3: Examples of prescribing and transcribing errors related to pADEs

NCC MERP category	E	F
Dosing error	The dosage of Oxycontin® (an opioid) was increased to a high dose at once instead of incrementally as required. The patient suffered from agitation.	An overdose of Fortum® (cephalosporin) led to a *Clostridium difficile* infection.
Therapeutic error	A high dosage of Diamicron® (an oral antidiabetic agent) was prescribed to a patient with renal failure. This resulted in hypoglycemia.	Oxybutynin (Driddase®) and tolterodine (Detrusitol®), both drugs for urge incontinence, were prescribed to one patient. The patient suffered from sedation and obstipation.
Transcribing error	On the administration chart, the frequency of a medication order for Selokeen® (beta blocker) was twice a day instead of once a day (prescribed). The patient suffered from hypotension.	The nurse transcribed a medication order for amoxicillin on the administration chart three days later than prescribed. The duration of the urinary tract infection was longer than it should be.

Most prescribing and transcribing errors did not reach patients (severity category B). Still a substantial number of the prescribing and transcribing errors reached patients but did not lead to an adverse drug event during their hospital stay (665 errors). The majority of errors that caused pADEs concerned temporary harm (category E) - for example constipation.

Preventable harm was caused by 1.8% of all medication errors or 1.4% of all medication orders. A total of 14.8% patients suffered from preventable harm related to medication errors in the prescribing or transcribing process. **(Figure 1)**

After adjusting for confounding factors in a multivariate analysis, therapeutic errors were more strongly associated with pADEs (odds ratio (OR)=1.98; 95% CI 1.53 to 2.56) than transcribing errors (OR=1.12; 95% CI 1.01 to1.25). **(Table 4)** In the multivariate analysis, dosing errors were not significantly associated with pADEs.

H	I
In the therapy to eradicate *Helicobacter Pylori*, the dose of Amoxicillin was too low en the duration of the proton pump inhibitor was too short. Thereafter the patient was re-admitted because of a bleeding ulcer.	An overdose of Fragmin® (low molecular weight heparin) was prescribed to a 91 year old woman. Thereafter she developed a cerebral vascular accident and died.

Table 4: Determinants of pADEs

Predictor	$OR_{unadjusted}$	95% CI	$OR_{adjusted}$*	95% CI
No. of dosing errors	**1.16****	**1.09–1.23**	1.05	0.92 – 1.21
No. of therapeutic errors	**2.22**	**1.77–2.78**	**1.98**	**1.53 – 2.56**
No. of transcription errors	**1.19**	**1.12–1.26**	**1.12**	**1.01 – 1.25**
Age:				
Lowest to 34	0.27	0.06–1.14		
35 to 49	0.51	0.21–1.23		
50 to 64	0.55	0.27–1.11		
65 to 79	1.26	0.75–2.10		
80 to highest	**2.00**	**1.22–3.25**	1.63	0.92 – 2.90
Gender (male is reference)	0.88	0.54-1.42		
No. of medication errors	**1.07**	**1.05–1.10**	0.98	0.90 – 1.05
No. of medication orders	**1.07**	**1.04–1.09**	1.00	0.96 – 1.05
Therapeutic area (ATC code):				
A10 (antidiabetics)	**2.24**	**1.23–4.08**	1.50	0.73 – 3.09
B01 (anticoagulants)	1.35	0.83–2.17		
B03 (drugs for anaemia)	**2.39**	**1.29–4.42**	**1.79**	0.86 – 3.71
H02 (corticosteroids	1.34	0.76–2.37		
J01 (antibiotics for systemic use)	**2.99**	**1.83–4.87**	1.48	0.82 – 2.68
M01 (anti-inflammatory drugs)	1.00	0.47–2.12		
N02 (analgesics)	**2.07**	**1.27–3.38**	1.30	0.72 – 2.32
N03 (antiepileptics)	1.11	0.37–3.31		
N05 (psycholeptics)	**2.16**	**1.33–3.50**	1.44	0.80 – 2.58
M04 (drugs for gout)	2.21	0.57–8.52		

*Adjusted for the confounding factors, which contributed significantly to the model,

** significant values are shown in bold

Discussion

Our study shows that approximately 2% of the medication errors related to the prescribing and transcribing process lead to pADEs. Of these errors, therapeutic errors are more strongly associated with pADEs than transcribing errors. Although we expected a relation between dosing errors and pADEs, a significant association could not be demonstrated. Dosing errors were errors like dosing too high or too low, but also errors like unclear or incomplete dosages. This last category of errors was usually corrected before reaching the patient and did not lead to preventable harm. This could explain the absence of a significant association between dosing errors and preventable harm. Though administrative errors are the most common errors made, no related harm could be detected. Most administrative errors did not reach patients, probably because they were intercepted by nurses or pharmacy staff through the various checking procedures in the prescribing process.

Earlier studies have already shown that prescribing errors are the most responsible for preventable harm.[3,9,20,21] Our study shows that this is particularly the result of therapeutic errors. By calculating odds ratios, this study provides an estimate of the magnitude of the risk, which builds on the previously conducted descriptive studies.

No other determinants of pADEs were found after adjustment for type of error, suggesting that the impact of the other included factors, such as high age (≥ 80) is 'mediated' through type of error.

In our study, the frequency of errors is extremely high; more than half of the medication orders contained one or more errors. Although high frequencies have been mentioned in literature,[22,23] the number of medication errors in our study is higher. Differences in definitions and methodology are possible explanations for these findings. In our opinion the very high error rates are primarily caused by the detailed classification scheme for medication errors. All kinds of administrative aspects (no administration route, missing of start date, etc.) were taken into account as errors. We defined these items as errors, while other studies did not. This clarifies to a large extent the high error rates. Our conclusion is, however, that these administrative errors do not (often) lead to patients being harmed. Nevertheless, removing these errors is still important for patient safety. Correction of administrative errors during the medication process can consume a substantial amount of time and effort and patient safety may be compromised indirectly because less time remains for identifying and correcting those types of errors that do result in patient harm. Furthermore, the correction procedures are at risk from human failures or weaknesses in the system.[24]

This study has several potential limitations. A weak point of this study is that the causality assessment was made by pharmacists only. No other healthcare professionals were involved in the assessment procedure (eg, physicians). Although the pharma-

cists in our study had broad clinical experience, a different clinical view from physicians could be expected. Nevertheless contrary to this expectation, Dean and Barber[25] showed that the reliability of the assessment of medication errors' severity was not affected by a rater's professional background, when enough assessors were included in the procedure (three or more). However, a group of raters including different professions might increase the acceptance of our findings by the different healthcare professionals.

Another limitation of our study is the lack of data on reliability between the investigators who collected data (eg, kappa values). However, we think that this issue may have had a limited effect on our study findings as we used the classification scheme for medication errors developed by the Netherlands Association of Hospital Pharmacists[12] that precisely defines specific types and subtypes of medication errors. The investigators individually assessed the medication of the same 10 patients and then discussed differences in classification. Furthermore, during the whole study period, the observers discussed on a regular basis how to collect and interpret data, and any extraordinary cases were classified in mutual agreement. This approach should have limited variability between the different investigators, but we have no objective means to tell if this assumption holds true.

In our study the number of pADEs may be over-rated because all adverse events with a possible relationship to a medication error have been taken into account. However, the results may also underestimate the extent of medication errors, because only adverse events occurring during the hospital stay were retrieved and not those occurring after a patient was discharged. Medication errors which reached patients during the hospital stay and did not immediately lead to patient harm could have the potential to do so in the future. For example, no gastric protection during the use of a combination of a NSAID and prednisolone usually does not lead immediately to a gastrointestinal bleeding, but could do so in the future.

Furthermore, only internal medicine, gastroenterology, rheumatology and geriatric medical units in two hospitals were studied, so the results may not apply to other medical specialities or to other hospitals.

Finally, this study considered medication errors in the process of prescribing and transcribing only.To provide a full overview of the extent to which medication errors can lead to harm, administration errors should be studied as well. Although studies have been conducted into the incidence and the potential severity of administration errors,[26,27] more research is needed to explore the association of administration errors with the occurrence of pADEs, specifically in comparison to the other types of medication errors.

One of the main strengths of this study is that it provides information not only on error frequencies, as many other studies do, but also on the associated frequency of actual patient harm. Another strength of this study is the prospective nature

and the use of an epidemiological design to determine potential associations between error type and ADEs.

To conclude, the findings indicate that a substantial percentage of the hospitalised patients suffer from pADEs due to prescribing and transcribing errors; in particular therapeutic errors (interactions, contra-indications, incorrect mono-therapy, duplicate therapy and errors on monitoring) are clinically relevant. Intervention and prevention programmes should focus on these medication errors. A Computerised Physician Order Entry System especially with a clinical decision support system could be a possible solution to reduce these types of medication errors.[28-30] Future research is needed to determine the impact of such interventions on the reduction in therapeutic errors and preventable patient harm as well as the cost-effectiveness of these interventions.

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Conflicts of interests

None declared.

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References

(1) *Institute of Medicine. To Err is Human: Building a Safer Health System. Washington, DC: National Academy Press; 1999.*

(2) *Institute of Medicine of the National Academies. http://www.iom.edu/ (accessed April 2007).*

(3) *Leape LL, Bates DW, Cullen DJ, et al. Systems analysis of adverse drug events. ADE Prevention Study Group. JAMA. 1995;274:35-43.*

(4) *Bates DW. Frequency, consequences and prevention of adverse drug events. J Qual Clin Pract. 1999;19:13-7.*

(5) Lisby M, Nielsen LP, Mainz J. Errors in the medication process: frequency, type, and potential clinical consequences. Int J Qual Health Care. 2005;17:15-22.

(6) Dean B, Schachter M, Vincent C, et al. Prescribing errors in hospital inpatients: their incidence and clinical significance. Qual Saf Health Care. 2002;11:340-4.

(7) Bates DW, Boyle DL, Vander Vliet MB, et al. Relationship between medication errors and adverse drug events. J Gen Intern Med. 1995;10:199-205.

(8) Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. JAMA. 1995;274:29-34.

(9) Kopp BJ, Erstad BL, Allen ME, et al. Medication errors and adverse drug events in an intensive care unit: direct observation approach for detection. Crit Care Med. 2006;34:415-25.

(10) Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse drug events in pediatric inpatients. JAMA. 2001;285:2114-20.

(11) Gurwitz JH, Field TS, Judge J, et al.The incidence of adverse drug events in two large academic long-term care facilities. Am J Med. 2005;118:251-8.

(12) Bemt van den PMLA, Egberts ACG. Drug-related problems: definitions and classifications. EJHP 2006;12(supl.):10-2.

(13) National Coordinating Council For Medication Error Reporting and Prevention. NCC MERP index for categorizing medication errors. http://www.nccmerp.org/ (accessed April 2007).

(14) Kramer MS, Leventhal JM, Hutchinson TA, et al. An Algorithm for the Operational Assessment of Adverse Drug Reactions. JAMA. 1979;242:623-32.

(15) Koch-Weser J, Sellers EM, Zacest R. The ambiguity of adverse drug reactions. Eur J Clin Pharmacol. 1977;11:75-8.

(16) Arimone Y, Begaud B, Miremont-Salame G, et al. Agreement of expert judgement in causality assessment of adverse drug reactions. Eur J Clin Pharmacol. 2005;61:169-73.

(17) Bemt van den PMLA, Fijn R, Voort van der PH, et al. Frequency and determinants of drug administration errors in the intensive care unit. Crit Care Med. 2002;30:846-50

(18) Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ. 2004;329: 15 -9.

(19) Leendertse A, Egberts ACG, Bemt van den PMLA. Hospital Admissions Related to Medication (HARM). Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University.; 2006.

(20) Bates DW, Teich JM, Lee J, et al. The impact of computerized physician order entry on medication error prevention. J Am Med Inform Assoc. 1999;6:313-21.

(21) Kanjanarat P, Winterstein AG, Johns TE, et al. Nature of preventable adverse drug events in hospitals: a literature review. Am J Health Syst Pharm. 2003;60:1750-9.

(22) *Bemt van den PM, Egberts TC, de Jong-van den Berg LT, et al. Drug-related problems in hospitalised patients. Drug Saf. 2000;22:321-33.*

(23) *Dean Franklin B, Vincent C, Schachter M, et al. The incidence of prescribing errors in hospital inpatients: an overview of the research methods. Drug Saf. 2005;28:891-900.*

(24) *Reason J. Human error: models and management. BMJ. 2000;320:768-70.*

(25) *Dean BS, Barber ND. A validated, reliable method of scoring the severity of medication errors. Am J Health Syst Pharm 1999;56:57-62*

(26) *Taxis K, Barber N. Incidence and severity of intravenous drug errors in a German hospital. Eur J Clin Pharmacol. 2004;59:815-7.*

(27) *Taxis K, Barber N. Ethnographic study of incidence and severity of intravenous drug errors. BMJ. 2003;326:684.*

(28) *Chaudhry B, Wang J, Wu S, et al. Systematic review: impact of health information technology on quality, efficiency, and costs of medical care. Ann Intern Med. 2006;144:742-52.*

(29) *Bates DW, Gawande AA. Improving safety with information technology. N Engl J Med. 2003;348:2526-34.*

(30) *Bates DW, Leape LL, Cullen DJ, et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. JAMA 1998;280:1311-6*

Chapter 4

Comparison of potential risk factors for medication errors with and without patient harm

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Abstract

Purpose

To compare determinants for medication errors leading to patient harm with determinants for medication errors without patient harm.

Methods

A two-way case-control design was used to identify determinants for medication errors without harm (substudy 1) and determinants for medication errors causing harm (substudy 2). Data of patients admitted to five internal medicine wards of two Dutch hospitals during five months were collected prospectively by chart review. Medication errors were detected and classified by two pharmacists. Consensus between five pharmacists was reached on the causal relationship between medication errors and patient harm. Data analysis was performed by multivariate logistic regression.

Results

We included 7286 medication orders, of which 3315 without errors (controls), and 5622 medication errors without harm (cases substudy 1) and 102 medication errors causing harm (cases substudy 2) were identified.

Hospital, ward and the therapeutic class anti-infectives were associated with both medication errors without harm (hospital odds ratio (OR) 1.40; 95% confidence interval (CI) 1.21-1.63), TweeSteden hospital (TSh) geriatrics OR 2.03; 95% CI 1.73-2.38, TSh general internal medicine OR 1.44; 95% CI 1.23-1.69 and anti-infectives OR 1.28; 95% CI 1.06-1.56) and medication errors with harm (hospital OR 4.91; 95% CI 3.02-7.79, TSh geriatrics OR 5.76; 95% CI 2.52-13.15, TSh general internal medicine OR 1.44; 95% CI 2.82-15.02 and anti-infectives OR 4.20; 95% CI 2.24-7.90).

Conclusions

This study shows that organisational determinants (hospital, ward) are comparable for medication errors with and without harm. For conclusions on patient- and medication related determinants studies with larger sample sizes are needed.

Introduction

The prevalence of medication errors in hospitals is about 6% of all medication orders and approximately 10% of all medication errors is estimated to result in patient harm.[1] Whether or not a medication error results in patient harm depends on whether the error reaches the patient and when it does, on the intrinsic toxicity of the drug and the susceptibility of the patient to adverse events. Also, certain types of medication errors are more likely to cause patient harm than others, e.g. therapeutic prescribing errors result in harm more often than administrative prescribing errors do.[2-5]

Despite the fact that not all medication errors lead to patient harm, the impact of the problem of adverse drug events (ADEs) induced by such errors is rather large. The report "To err is human" showed that in the United States 2% of all admitted patients is harmed as a result of a medication error and that 7000 patients die from medication errors annually.[6] This report has led to a renewed interest of health care professionals in improving medication safety. Such improvements can be achieved by effective interventions targeted at identified risk factors that contribute to unsafe practices and potential patient harm.

Whereas preventing actual patient harm is the ultimate goal of such medication safety initiatives, medication errors are often used as a surrogate outcome measure, because these occur more frequently and are easier to detect. However, the validity of this surrogate end point has not been established and it is unknown whether the risk factors associated with medication errors causing patient harm are the same as the risk factors associated with medication errors that do not cause harm. Therefore, we performed a study to compare the determinants for medication errors resulting in patient harm and the determinants for medication errors not resulting in harm.

Methods

Design and setting

The design of the current study is a two-way case-control study. In a first substudy (1st way) medication orders with errors not leading to patient harm (cases) were compared to medication orders without errors (controls). This first substudy aimed to identify determinants for medication errors not leading to patient harm. In the second substudy (2nd way) medication orders with errors leading to patient harm (cases) were again compared to the same medication orders without errors (controls) to identify determinants for medication errors leading to patient harm. Subsequently, determinants that were identified in the first substudy were compared with determinants identified in the second substudy.

This study is part of the POEMS study on the effect of a Computerised Physician Order Entry (CPOE) system on Medication Safety and associated costs.[5, 7] The POEMS study is a prospective intervention study, performed in two medical wards (one geriatric and one general internal medicine ward) of the 600 bed teaching hospital "TweeSteden" (TSh) in Tilburg and Waalwijk and three medical wards (two general internal medicine wards and one gastroenterology/rheumatology ward) of the 1300 bed University Medical Center in Groningen (UMCG), the Netherlands. The current study uses data of the period before the introduction of the CPOE-system. The process of medication ordering and administration consisted of a hand-written system: physicians prescribed medication orders on charts and nurses transcribed these medication orders on administration charts.

Patients

From July through November 2005 all patients admitted to the study wards for more than 24 hours were included. Patients received written information about the study after which they could object to inclusion. A waiver of the Medical Ethical Committee was obtained for this study, as the study fell within the boundaries of normal hospital care and routine of quality improvement and assurance.

Data collection

During ward visits the investigators prospectively extracted patients' characteristics (age, sex, weight and length) and data on diseases (medical history, reasons for admission and diagnoses) and adverse events (i.e. untoward medical occurrences which do not have to have a causal relationship with the treatment[8]) from medical records. Medication orders during hospitalisation were collected by reviewing medication order charts and administration charts. Medication errors were identi-

fied by two pharmacists. For ethical reasons, the physician was informed in case of potentially life threatening errors that were discovered during the process of data collection. These errors were not excluded from the study.

Classification of prescribing and transcribing errors

Medication errors were categorised by two pharmacists according to the classification scheme for medication errors developed by the Dutch Association of Hospital Pharmacists.[9] This classification distinguishes prescribing, transcribing, dispensing, administering and "across settings" errors. In this study only prescribing and transcribing errors were recorded. Prescribing errors are subdivided into administrative errors (errors on readability, patient data, ward and prescriber data, drug name, dosage form and route of administration), dosing errors (errors on strength, frequency, dosage, length of therapy and directions for use) and therapeutic errors (interactions, contra-indications, incorrect mono-therapy, duplicate therapy and errors on therapeutic drug monitoring or laboratory monitoring). inappropriate drug choices were not actively assessed and were only taken into account when they were obvious. Transcribing errors are defined as errors in the process of interpreting, verifying and transcribing of medication errors. The severity of all medication errors was assessed according to the index of the National Coordinating Council for Medication Error Reporting and Preventing (NCC MERP).[10]
In this study, medication errors were divided into errors that did not lead to patient harm (NCC MERP category B up to D) and errors that did lead to harm (NCC MERP category E up to I).

Patient harm

Patient harm was defined as a preventable adverse drug event (pADE) which is an adverse drug event that occurred due to a medication error with a possible or probable causal relationship with the medication error. To assess this relationship an algorithm was developed, based on the NCC MERP index and the Yale algorithm.[7, 10, 11] The first three items of the Yale algorithm were used: knowledge about the relation between the drug and the event, the presence of underlying clinical conditions which could be responsible for the event and the timing of the event. The causal relations between all medication errors made and the adverse events extracted from the medical records were assessed by five pharmacists. After individual assessment consensus was reached for all cases on both causality and severity. The causal relationship could be defined as unlikely (score < 0), possible (score ≥ 0 and ≤ 3) or probable (score $= 4$). An event was defined as patient harm when consensus was reached on a possible or probable relationship with the medication error.

Determinants

Potential determinants of medication errors with and without patient harm that were studied included organisational characteristics (hospital, ward, transfer from another hospital ward or care institution, length of stay and readmission to study ward during study period), patient characteristics (gender, age, renal impairment (defined as creatinine clearance ≤ 50 ml/min during hospitalisation) and the number of medication orders per patient during hospital stay), characteristics of the medication order (weekday of prescription, dosage frequency less than once daily and route of administration) and the therapeutic area of the medication (identified by Anatomical-Chemical-Therapeutic (ATC) code).

Data analysis

All data were processed with MS Access 2003 and analysed with SPSS version 16.0.

Determinants for medication errors that did not lead to patient harm were identified by comparing medication orders containing these errors with medication orders without errors (substudy 1). Determinants for medication errors that resulted in patient harm were identified by comparing medication orders containing these errors with medication orders without errors (substudy 2). Univariate logistic regression analysis was performed with the medication order as unit of analysis. Multiple errors could have been made in one medication order and analysis was performed for each medication error separately.

For determinants that were statistically significantly associated ($p<0.05$) with errors in the univariate analysis, a multivariable logistic regression analysis was performed using a stepwise forward logistic regression model. Determinants were included in the model when they changed the beta coefficient with at least 10%. Crude and adjusted odds ratios with 95% confidence intervals were calculated. Determinants that were significantly associated with medication errors without harm in substudy 1 were compared to determinants for medication errors leading to patient harm identified in substudy 2.

Results

During data collection 558 patients were included and 4 patients were excluded from the study due to objection to inclusion. Since 28 patients were re-admitted once and three patients were re-admitted twice, 592 admissions were included in the study. During these admissions 7286 medication orders were prescribed of which 3315 contained no error (controls). In the other 3971 medication orders a total of 5724 medication errors were identified of which 5622 did not cause patient harm (cases substudy 1) and 102 resulted in patient harm (cases substudy 2)

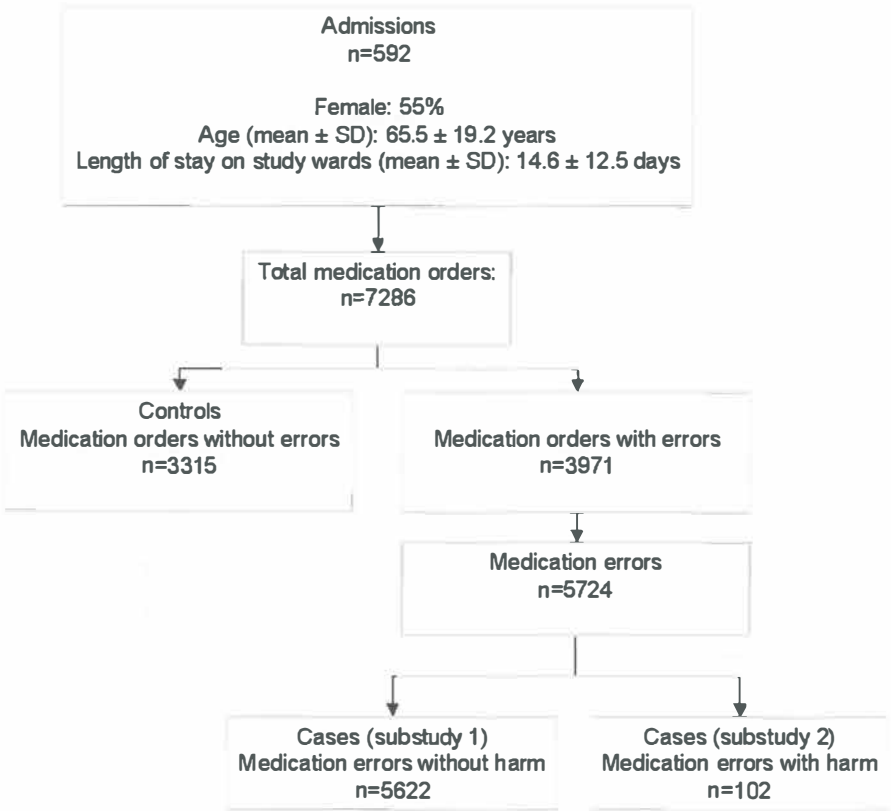

Figure 1: Patient characteristics, medication orders and medication errors

(Figure 1). Nine medication errors were considered serious enough to require an intervention by the investigators to preclude harm. These errors were classified as errors that did not result in patient harm, but which required interventions to preclude harm (NCC MERP category D).

Details of the univariate and multivariate analysis of organisational characteristics, patient characteristics, characteristics of the medication order and the therapeutic area are presented in tables 1 to 4.
After multivariate analysis the following determinants were significantly associated with medication errors without patient harm: hospital, ward, transfer of patient, length of hospital stay, number of medication orders per patient during hospital stay, weekday of the prescription, route of administration and the therapeutic classes cardiovascular tract, genitourinary system and hormonal system, hormonal systemic therapy, anti-infectives, musculoskeletal system, nervous system and respiratory tract.

Of these determinants the following were also statistically significantly associated with medication errors with harm: hospital, ward and therapeutic class anti-infectives.
All other determinants that were statistically significantly associated with medication errors without harm (transfer of patient, length of hospital stay, number of medication orders per patient, day of prescription, route of administration and the other therapeutic classes) showed no association with medication errors with harm in the univariate analysis already, had insufficient cases per category to analyse the association or showed a different trend in the odds ratio. No determinants for medication errors leading to harm were identified that had not been identified as determinant for medication errors without harm.

Table 1: Organisational characteristics associated with medication errors with and without patient harm after univariate logistic regression (odds ratios) and multivariate logistic regression (adjusted odds ratios)

			Medication errors without harm (substuc		
Potential determinant	**Cases n (%)**	**Controls n (%)**	**OR**	**95% CI**	**OR**
Hospital					
TSh (UMCG is reference)	3468 (61.7)	1459 (44.0)	**2.05**	**1.88-2.24**	**1.4**
Ward					
UMCG General internal medicine	904 (16.1)	732 (22.1)	ref		re
UMCG Gastroenterology/ rheumatology	1250 (22.2)	1124 (33.9)	0.90	0.79-1.02	0.9
TSh Geriatrics	2250 (40.0)	796 (24.0)	**2.29**	**2.02-2.60**	**2.0**
TSh General internal medicine	1218 (21.7)	663 (20.0)	**1.49**	**1.30-1.70**	**1.4**
Transfer from: (n=8255/ n=3056)					
Home (ref)	3175 (60.1)	1566 (52.7)	ref		re
Another hospital ward	446 (8.4)	254 (8.5)	0.87	0.73-1.02	**0.6**
Care institution	1663 (31.5)	1151 (38.7)	**0.71**	**0.65-0.79**	**0.8**
Length of stay (days, mean ± SD)*	22.2 ± 17.0	19.2 ± 15.5	**1.01**	**1.01-1.02**	**1.0**
Readmission	360 (6.4)	233 (7.0)	0.91	0.76-1.07	

Figures in bold are statistically significant

Abbreviations: OR, odds ratio; 95 %CI, 95% confidence interval; ORadj , adjusted odds ratio; TSh, TweeSteden hospital; UMCG, University Medical Centre Groningen; ref, reference

1: Adjusted for ward, transfer and day of prescription

2: No confounding factors were identified

3: Adjusted for transfer, length of stay, age group, renal impairment, number of medication orders, day of prescription, hospital initiated drug and pharmacotherapeutic area

4: Adjusted for age and pharmacotherapeutic area

5: Adjusted for hospital, ward and length of stay

6: Adjusted for number of medication orders

* Analysed as a continuous variable

	Medication errors with harm (substudy 2)					
95% CI	**Cases n (%)**	**Controls n (%)**	**OR**	**95% CI**	**OR_{adj}**	**95% CI**
.21-1.63	**81 (79.4)**	**1459 (44.0)**	**4.91**	**3.02-7.97**	**4.91[2]**	**3.02-7.97**
	7 (6.9)	732 (22.1)	ref		ref	
.79-1.08	14 (13.7)	1124 (33.9)	1.30	0.52-3.24	1.73[4]	0.68-4.41
.73-2.38	**49 (48.0)**	**796 (24.0)**	**6.44**	**2.90-14.30**	**5.76[4]**	**2.52-13.15**
.23-1.69	**32 (31.4)**	**663 (20.0)**	**5.05**	**2.21-11.51**	**6.51[4]**	**2.82-15.02**
	56 (59.6)	1566 (52.7)	ref			
.58-0.81	9 (9.6)	254 (8.5)	0.99	0.48-2.02		
.78-0.96	29 (30.9)	1151 (38.7)	0.71	0.45-1.11		
.01-1.02	20.4 ± 11.7	19.2 ± 15.5	1.00	0.99-1.02		
	8 (7.8)	233 (7.0)	1.13	0.54-2.35		

Table 2: Patient characteristics associated with medication errors with and without patient harm after univariate logistic regression (odds ratios) and multivariate logistic regression (adjusted odds ratios)

		Medication errors without harm (substuc			
Potential determinant	**Cases n (%)**	**Controls n (%)**	**OR**	**95% CI**	**OR_{adj}**
Female gender (male is reference)	2990 (53.2)	1780 (53.7)	0.98	0.90-1.07	
Age (years, mean ± SD)*	70.8 ± 16.8	67.1 ± 17.8	**1.01**	**1.01-1.02**	1.00[1]
<50 years	778 (13.8)	605 (18.3)	ref		ref
50 t/m 64 years	882 (15.7)	668 (20.2)	1.03	0.89-1.19	1.00[3]
65 t/m 79 years	1859 (33.1)	1053 (31.8)	**1.38**	**1.21-1.56**	0.99[4]
≥ 80 years	2103 (37.4)	989 (29.8)	**1.65**	**1.45-1.88**	1.02[5]
Renal impairment	3176 (56.5)	1700 (51.3)	**1.23**	**1.13-1.34**	1.03[6]
Number of medication orders (mean ± SD)*	19.2 ± 17.0	18.2 ± 10.7	**1.01**	**1.00-1.01**	**0.99**
Polyfarmacy (>4)	5534 (98.4)	3253 (98.1)	1.20	0.86-1.66	

Figures in bold are statistically significant

Abbreviations: OR, odds ratio; 95 %CI, 95% confidence interval; OR_{adj}, adjusted odds ratio

1: Adjusted for hospital, ward, length of stay and pharmacotherapeutic area

2: Adjusted for hospital

3: Adjusted for hospital, ward, transfer, length of stay, renal impairment, number of medication orders, day of prescription, route of administration and pharmacotherapeutic area

4: Adjusted for hospital, ward and pharmacotherapeutic area

5: Adjusted for hospital, ward, transfer, length of stay, age, number of medication orders, day of prescription, route of administration and pharmacotherapeutic area

6: Adjusted for hospital, ward, transfer, length of stay, day of prescription, route of administration and pharmacotherapeutic area

* Analysed as a continuous variable

§ Dummy variables included

	Medication errors with harm (substudy 2)					
)5% CI	**Cases n (%)**	**Controls n (%)**	**OR**	**95% CI**	**OR_{adj}**	**95% CI**
	47 (46.1)	1780 (53.7)	0.74	0.50-1.10		
00-1.01	74.1 ± 14.8	67.1 ± 17.8	**1.03**	**1.01-1.04**	1.01[2]	1.00-1.03
	9 (8.8)	605 (18.3)	ref		ref	
85-1.18	12 (11.8)	668 (20.2)	1.21	0.51-2.89	1.35[4]	0.56-3.26
84-1.17	38 (37.3)	1053 (31.8)	**2.43**	**1.17-5.05**	1.77[4]	0.81-3.90
85-1.23	43 (42.2)	989 (29.8)	**2.92**	**1.42-6.04**	1.74[4]	0.76-4.02
92-1.16	61 (59.8)	1700 (51.3)	1.41	0.95-2.11		
99-1.00	18.3 ± 9.1	18.2 ± 10.7	1.00	0.98-1.02		
	103 (99.0)[5]	3254 (98.1)[5]	1.99	0.27-14.52		

Table 3: Characteristics of the medication order associated with medication errors with and without patient harm after univariate logistic regression (odds ratios) and multivariate logistic regression (adjusted odds ratios)

		Medication errors without harm (substu			
Potential determinant	**Cases n (%)**	**Controls n (%)**	**OR**	**95% CI**	**OR**
Day of prescription (n=8899/3398)					
Monday	959 (17.1)	631 (19.1)	ref		re
Tuesday	871 (15.5)	559 (17.0)	1.03	0.89-1.19	1.0
Wednesday	971 (17.3)	557 (16.9)	1.15	0.99-1.33	1.1
Thursday	951 (17.0)	530 (16.1)	**1.18**	**1.02-1.37**	1.0
Friday	1120 (20.0)	587 (17.8)	**1.26**	**1.09-1.45**	**1.2**
Saturday	352 (6.3)	203 (6.2)	1.14	0.93-1.40	**1.2**
Sunday	378 (6.7)	230 (7.0)	1.08	0.89-1.31	1.1
Weekend (*weekdays are reference*)	730 (13.0)	433 (13.1)	0.99	0.87-1.13	
Dosage frequency < once daily	163 (2.9)	83 (2.5)	1.16	0.89-1.52	
Route of administration					
Oral	3701 (65.8)	2346 (70.8)	ref		re
Topical	94 (1.7)	35 (1.1)	**1.70**	**1.15-2.52**	2.1
Inhalation	209 (3.7)	66 (2.0)	**2.01**	**1.52-2.66**	1.7
Dermal	123 (2.2)	19 (0.6)	**4.10**	**2.52-6.67**	**3.3**
Parenteral	1121 (19.9)	758 (22.9)	0.94	0.84-1.04	1.0
Rectal	280 (5.0)	62 (1.9)	**2.86**	**2.16-3.79**	**3.1**
Transdermal	55 (1.0)	29 (0.9)	1.20	0.76-1.89	0.9
Sublingual	39 (0.7)	0 (0.0)	†		

Figures in bold are statistically significant

Abbreviations: OR, odds ratio; 95 %CI, 95% confidence interval; OR_{adj}, adjusted odds ratio ref, reference

1: Adjusted for hospital, ward, length of stay, route of administration and pharmacotherapeutic area

4: Adjusted for hospital, ward, transfer, length of stay, number of medication orders, day of prescription and pharmacotherapeutic area

† Statistical analysis not possible due to insufficient data

§ Dummy variables included

	Medication errors with harm (substudy 2)					
95% CI	**Cases n (%)**	**Controls n (%)**	**OR**	**95% CI**	**OR_{adj}**	**95% CI**
	18 (17.8)	631 (19.1)	ref			
0.88-1.20	15 (14.9)	559 (17.0)	0.94	0.47-1.88		
0.94-1.27	21 (20.8)	557 (16.9)	1.32	0.70-2.51		
0.93-1.26	20 (19.8)	530 (16.1)	1.32	0.70-2.53		
1.05-1.41	18 (17.8)	587 (17.8)	1.08	0.55-2.09		
1.04-1.57	7 (6.9)	203 (6.02)	1.21	0.50-2.94		
0.96-1.43	2 (2.0)	230 (7.0)	0.31	0.07-1.32		
	9 (8.9)	433 (13.1)	0.65	0.32-1.29		
	1 (1.0) §	84 (2.5) §	0.37	0.05-2.71		
	72 (70.6)	2346 (70.8)	ref			
0.99-4.62	1 (1.0)	35 (1.1)	0.93	0.13-6.89		
0.71-1.92	4 (3.9)	66 (2.0)	1.98	0.70-5.57		
.31-8.41	0 (0)	19 (0.6)	†			
0.91-1.18	23 (22.5)	758 (22.9)	0.99	0.61-1.59		
.33-4.37	2 (2.0)	62 (1.9)	1.05	0.25-4.38		
0.52-1.57	0 (0)	29 (0.9)	†			
	0 (0)	0 (0)	†			

Table 4: Therapeutic areas associated with medication errors with and without patient harm after univariate logistic regression (odds ratios) and multivariate logistic regression (adjusted odds ratios)

	Medication errors without harm (substu				
Potential determinant	**Cases n (%)**	**Controls n (%)**	**OR**	**95% CI**	**OR_{adj}**
Therapeutic area (ATC-code)					
Gastrointestinal tract (A)	1166 (20.7)	835 (25.2)	ref		ref
Blood system (B)	691 (12.3)	478 (14.4)	1.04	0.89-1.20	1.13[1]
Cardiovascular tract (C)	831 (14.8)	716 (21.6)	**0.83**	**0.73-0.95**	**0.82[1]**
Dermatologicals (D)	124 (2.2)	24 (0.7)	**3.70**	**2.37-5.78**	1.45[1]
Genitourinary system and sex hormones (G)	35 (0.6)	40 (1.2)	**0.63**	**0.40-0.995**	**0.59[1]**
Hormonal systemic therapy (H)	249 (4.4)	126 (3.8)	**1.42**	**1.12-1.79**	**1.63[1]**
Anti-infectives (J)	454 (8.1)	264 (8.0)	**1.23**	**1.03-1.47**	**1.28[1]**
Cancer therapy (L)	47 (0.8)	47 (1.4)	0.72	0.47-1.08	0.81[1]
Musculo-skeletal system (M)	172 (3.1)	86 (2.6)	**1.43**	**1.09-1.89**	**1.62[1]**
Nervous system (N)	1415 (25.2)	537 (16.2)	**1.89**	**1.65-2.16**	**1.85[1]**
Antiparasitic products, insecticides and repellents (P)	5 (0.1)	13 (0.4)	**0.28**	**0.10-0.78**	0.40[1]
Respiratory tract (R)	324 (5.8)	104 (3.1)	**2.23**	**1.76-2.83**	**2.30[1]**
Sensory organs (S)	68 (1.2)	28 (0.8)	**1.74**	**1.11-2.73**	0.92[1]
Various (V)	36 (0.6)	13 (0.4)	**1.98**	**1.05-3.76**	1.11[1]
Unknown	5 (0.1)	4 (0.1)	0.90	0.24-3.34	1.02[1]

Figures in bold are statistically significant

Abbreviations: OR, odds ratio; 95 %CI, 95% confidence interval; ORadj , adjusted odds ratio; ref, reference

1: Adjusted for hospital, ward, transfer, length of stay, day of prescription and route of administration

2: Adjusted for hospital, ward and age

† Statistical analysis not possible due to insufficient data

	Medication errors with harm (substudy 2)					
95% CI	**Cases n (%)**	**Controls n (%)**	**OR**	**95% CI**	**OR_{adj}**	**95% CI**
	20 (19.6)	835 (25.2)	ref		ref	
0.95-1.33	14 (13.7)	478 (14.4)	1.22	0.61-2.44	1.22	0.60-2.45
).71-0.94	10 (9.8)	716 (21.6)	0.58	0.27-1.25	0.48	0.22-1.03
0.59-3.53	0 (0)	24 (0.7)	†		†	
).36-0.96	1 (1.0)	40 (1.2)	1.04	0.14-7.97	0.84	0.11-6.51
.26-2.10	1 (1.0)	126 (3.8)	0.33	0.04-2.49	0.37	0.05-2.77
.06-1.56	23 (22.5)	264 (8.0)	**3.64**	**1.97-6.73**	**4.20[2]**	**2.24-7.90**
0.49-1.35	0 (0)	47 (1.4)	†		†	
.20-2.20	2 (2.0)	86 (2.6)	0.97	0.22-4.22	1.08	0.25-4.75
.60-2.14	25 (24.5)	537 (16.2)	**1.94**	**1.07-3.53**	1.62[2]	0.89-2.98
0.14-1.18	0 (0)	13 (0.4)	†		†	
.54-3.43	5 (4.9)	104 (3.1)	2.01	0.74-5.46	2.15	0.78-5.94
0.38-2.21	1 (1.0)	28 (0.8)	1.49	0.19-11.51	1.56	0.19-12.50
0.51-2.42	0 (0)	13 (0.4)	†		†	
0.23-4.59	0 (0)	4 (0.1)	†		†	

Discussion

This study is the first study on the comparison of determinants for medication errors with and without consequent patient harm.
Hospital, ward and the therapeutic class of anti-infectives were shown to be determinants for both types of medication errors.
In this study relatively few medication errors causing patient harm were identified, despite the collection of more than 7000 medication orders during five months of daily ward visits, This main limitation of our study may explain why many of the determinants that were identified in the multivariate analysis for medication errors without harm, were non-significant in the univariate analysis for medication errors with harm.
The determinants hospital and ward point in the same direction, namely that errors (either with or without harm) probably occur more often in the TSh than in the UMCG. Thus, even after correction for case-mix, it remains likely that the personnel or local processes influence the prevalence of errors, irrespective of the outcome. Therefore, it may be concluded that for these organisational determinants, medication errors are an acceptable surrogate outcome measure for patient harm. This corresponds with findings of previous studies separately showing that organisational determinants are linked to respectively medication errors and pADEs. [2,4,12-15]
Due to the limited power of our study for medication errors leading to harm, definite conclusions on determinants that are more patient- or medication related can not be drawn, with the possible exception of anti-infectives. Theoretically it seems likely that for medication errors leading to patient harm, specific determinants may be identified that reflect either the vulnerability of the patient to experience preventable adverse drug events or the intrinsic toxicity of the medication. Again, the determinants identified in our study for medication errors without harm were identified in other studies, both for medication errors (identified determinants were number of medication orders per patient, route of administration and pharmacotherapeutic area[1,16,17]) and for (preventable) ADEs (identified determinants were among others number of medication orders per patient and therapeutic area[1,13,15,17-20]). However, none of these previous studies compared the determinants for medication errors without harm with the determinants for medication errors leading to patient harm.
Besides the small sample size of medication errors leading to harm, this study has several other limitations. First, only five wards in two hospitals were studied, so the results cannot be generalised to other medical specialties, wards or hospitals. Second, the medication ordering was done in the context of a handwritten-system. Implementation of a computerised physician order entry system with clinical decision support could change the risk factors for medication errors. Third, risk factors

for medication errors and consequent harm could differ between continuation of pre-admission treatment and hospital-initiated drugs. Because it wasn't necessary to define pre-admission treatment in the POEMS-study, this determinant could not be included in this study either. Finally, only prescribing and transcribing errors were considered in this study. To provide a full overview of the potential determinants for medication errors with and without harm distribution errors, administration errors and across setting errors should also be studied.

The main strength of this study is the epidemiological approach to identify risk factors by calculating odds ratios, whereas many other studies used error frequencies. Moreover, we established the actual outcome of the medication error instead of the potential harm an error could cause which many other studies did and our study is the first comparing determinants for medication errors without and with patient harm.

Future research with a larger sample size of medication errors leading to patient harm is recommended. These future studies should also take into account other types of medication errors and include more organisational determinants (such as the use of electronic prescribing) and patient related factors (like the reason for admission and comorbidities).

Conclusion

To conclude, medication errors resulting in harm and medication errors without harm have some determinants in common, which are mainly on the organisational level. Therefore, the present study gives a first direction about the validity of medication errors as a surrogate outcome measure when looking at these organisational aspects. More determinants could possibly be identified in studies with larger sample sizes, which may identify specific patient- and medication related determinants for medication errors leading to patient harm.

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References

1. *Krahenbuhl-Melcher A, Schlienger R, Lampert M, et al. Drug-related problems in hospitals: a review of the recent literature. Drug Saf 2007; 30: 379-407*
2. *Bates DW. Frequency, consequences and prevention of adverse drug events. J Qual Clin Pract 1999; 19: 13-7*

3. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. Jama 1995; 274: 29-34
4. Leape LL, Bates DW, Cullen DJ, et al. Systems analysis of adverse drug events. ADE Prevention Study Group. Jama 1995; 274: 35-43
5. van Doormaal JE, van den Bemt PMLA, Mol PGM, et al. Medication errors: the impact of prescribing and transcribing errors on preventable harm in hospitalised patients. Qual Saf Health Care 2009; 18: 22-7
6. Institute of Medicine. To err is human: building a safer health system: National Academy Press. Washington DC; 2000; 312.
7. Van Doormaal JE, Mol PGM, Van den Bemt PMLA, et al. Reliability of the assessment of preventable adverse drug events in daily clinical practice. Pharmacoepidemiol Drug Saf 2008; 17: 645-54
8. The Uppsala Monitoring Centre. Glossary of terms used in Pharmacovigilance. http://www.who-umc.org/graphics/15338.pdf.
9. Van den Bemt PMLA and Egberts ACG. Drug-related problems: definitions and classifications. EJHP Practice 2007; 13: 62-64
10. National Coordinating Council for Medication Error Reporting and Preventing. NCC MERP index for categorizing medication errors. http://www.nccmerp.org/pdf/indexColor2001-06-12.pdf.
11. Kramer MS, Leventhal JM, Hutchinson TA, et al. An algorithm for the operational assessment of adverse drug reactions. Background, description, and instructions for use. Jama 1979; 242: 623-32
12. Dean B, Schachter M, Vincent C, et al. Causes of prescribing errors in hospital inpatients: a prospective study. Lancet 2002; 359: 1373-8
13. Kanjanarat P, Winterstein AG, Johns TE, et al. Nature of preventable adverse drug events in hospitals: a literature review. Am J Health Syst Pharm 2003; 60: 1750-9
14. Lesar TS, Briceland L and Stein DS. Factors related to errors in medication prescribing. Jama 1997; 277; 312-7
15. Bates DW, Miller EB, Cullen DJ, et al. Patient risk factors for adverse drug events in hospitalized patients. ADE Prevention Study Group. Arch Intern Med 1999; 159: 2553-60
16. Fijn R, Van den Bemt PMLA, Chow M, et al. Hospital prescribing errors: epidemiological assessment of predictors. Br J Clin Pharmacol 2002; 53: 326-31
17. Leendertse AJ, Egberts ACG, Stoker LJ, et al. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med 2008; 168: 1890-6
18. Evans RS, Lloyd JF, Stoddard GJ, et al. Risk factors for adverse drug events: a 10-year analysis. Ann Pharmacother 2005; 39: 1161-8
19. Van den Bemt PMLA, Egberts ACG, Lenderink AW, et al. Risk factors for the development of adverse drug events in hospitalized patients. Pharm World Sci 2000; 22: 62-6
20. Von Laue NC, Schwappach DL and Koeck CM. The epidemiology of preventable adverse drug events: a review of the literature. Wien Klin Wochenschr 2003; 115: 407-15

Part II Chapter 5

The influence that computerised prescribing has on medication errors and preventable adverse drug events: an interrupted time-series study

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Abstract

Objective

This study will evaluate the effect of a Computerised Physician Order Entry system with basic Clinical Decision Support (CPOE/CDSS) on the incidence of medication errors (MEs) and preventable adverse drug events (pADEs).

Design

Interrupted time-series design

Measurements

The primary outcome measurements are comprised of the percentage of medication orders with one or more MEs and the percentage of patients with one or more pADEs.

Results

Pre-implementation, the mean percentage of medication orders containing at least one ME was 55%, whereas this became 17% post-implementation. The introduction of CPOE/CDSS has led to a significant immediate absolute reduction of 40.3% (95%CI:-45.13%;-35.48%) in medication orders with one or more errors.
Pre-implementation, the mean percentage of admitted patients experiencing at least one pADE was 15.5%, as opposed to 7.3% post-implementation. However, this decrease could not be attributed to the introduction of CPOE/CDSS: the immediate change was not significant (-0.42%, 95% CI:-15.52%; 14.68%) because of the observed underlying negative trend during the pre-CPOE period of -4.04% (95% CI: -7.70%; -0.38%) per month.

Conclusion

This study has shown that CPOE/CDSS reduces the incidence of medication errors and thus indirectly has a positive effect on the potential risk for patient harm. However, a direct effect on actual patient harm (pADEs) could not be demonstrated.

Introduction

Since the publication of the Institute of Medicine (IOM) report, "To Err is Human," many strategies for making health care safer have been created and implemented.[1] One of these strategies is computerised prescribing through the use of a Computerised Physician Order Entry (CPOE) system. Before the first introduction of this system in the United States in the 1990s, expectations about CPOE systems reducing medication errors and patient harm were high. Legibility and completeness of prescriptions would be ensured[2] and Clinical Decision Support Systems (CDSS) incorporated in the CPOE systems would be able to assist physicians by triggering alerts in case of drug-drug interactions and inappropriate dosing. These were all reasons to suppose that CPOE/CDSS systems would be effective in reducing medication errors and adverse drug events, and thereby improving medication safety.

Meanwhile, a number of studies (predominantly from the US) showed that CPOE/CDSS systems were indeed successful strategies for reducing medication errors, and there was some indication of patient harm being reduced.[3-9] Other studies showed negative effects in the sense that new medication errors were being introduced through CPOE/CDSS[10] or that mortality increased after implementation of CPOE/CDSS in a children's hospital.[11] However, most of these CPOE/CDSS studies used a pre/post analysis to evaluate the effect. This is not a robust study design, because it does not take into account other factors during the introduction and eventual use of CPOE/CDSS that might explain the change in outcome. An interrupted time-series (ITS) design with segmented linear regression analysis is more robust, because it evaluates the longitudinal effect of CPOE/CDSS and controls for trends in the outcome.[12]

Moreover, studies that looked into the effect of computerised prescribing were predominantly performed in the USA, because it was here that CPOE/CDSS was first introduced into clinical practice. The findings from these studies may not apply to the European hospital setting due to differences in computer systems and work processes between the two continents. Finally, most studies were monocenter studies, which makes generalisability to other hospital settings low.

Therefore, this study has used an ITS design with segmented linear regression analysis in order to evaluate the effect that CPOE/CDSS has had on the incidence of medication errors and to relate this to patient harm in two Dutch hospitals.

Methods

Setting and study population

This study was performed in two medical wards of the 1300-bed University Medical Center Groningen (a general internal medicine and a gastroenterology/rheumatology ward) and in two medical wards (a geriatric and a general internal medicine ward) of the 600-bed teaching hospital "TweeSteden" in Tilburg and Waalwijk, the Netherlands. All patients admitted to these wards for more than 24 hours were included. A waiver of the Medical Ethical Committee was obtained for this study, as the study fell within the boundaries of quality of care improvement. Patients received information about the study and they could decline to participate.

Design

The study was set up as an interrupted time series that is characterised by a series of measurements over time interrupted by an intervention. In this study the intervention was the implementation of a Computerised Physician Order Entry system in combination with a basic Clinical Decision Support System (CPOE/CDSS). Data collection took place during a five-month pre-implementation period (during which the hand-written medication order system continued to be used) and during a five-month post-implementation period (when the CPOE/CDSS system continued to be used). The post-implementation data collection period started eight weeks after finishing the implementation process in order to make sure that initial problems were solved. Because CPOE/CDSS was not simultaneously implemented in all study wards, the starting date for the post-implementation period was different for each ward.

In both hospitals, pre-implementation data were collected from July through November 2005 (Figure A). In the TweeSteden hospital, the post-implementation data collection on the geriatric ward was from April through August 2006, and on the general internal medicine ward from mid-June through mid-November 2006. In the University Medical Center Groningen, the post-implementation period on the general internal medicine ward was from August through December 2006. Post-implementation data collection on the gastroenterology/rheumatology ward was planned from September 2006 through January 2007, but, due to the delay in implementation of CPOE/CDSS, this period was postponed to January through May 2008. CPOE was implemented per ward, that is, simultaneously for all hospital beds in that ward. Post-implementation data collection for each ward started eight weeks after CPOE was implemented and lasted for five months for all beds in each ward.

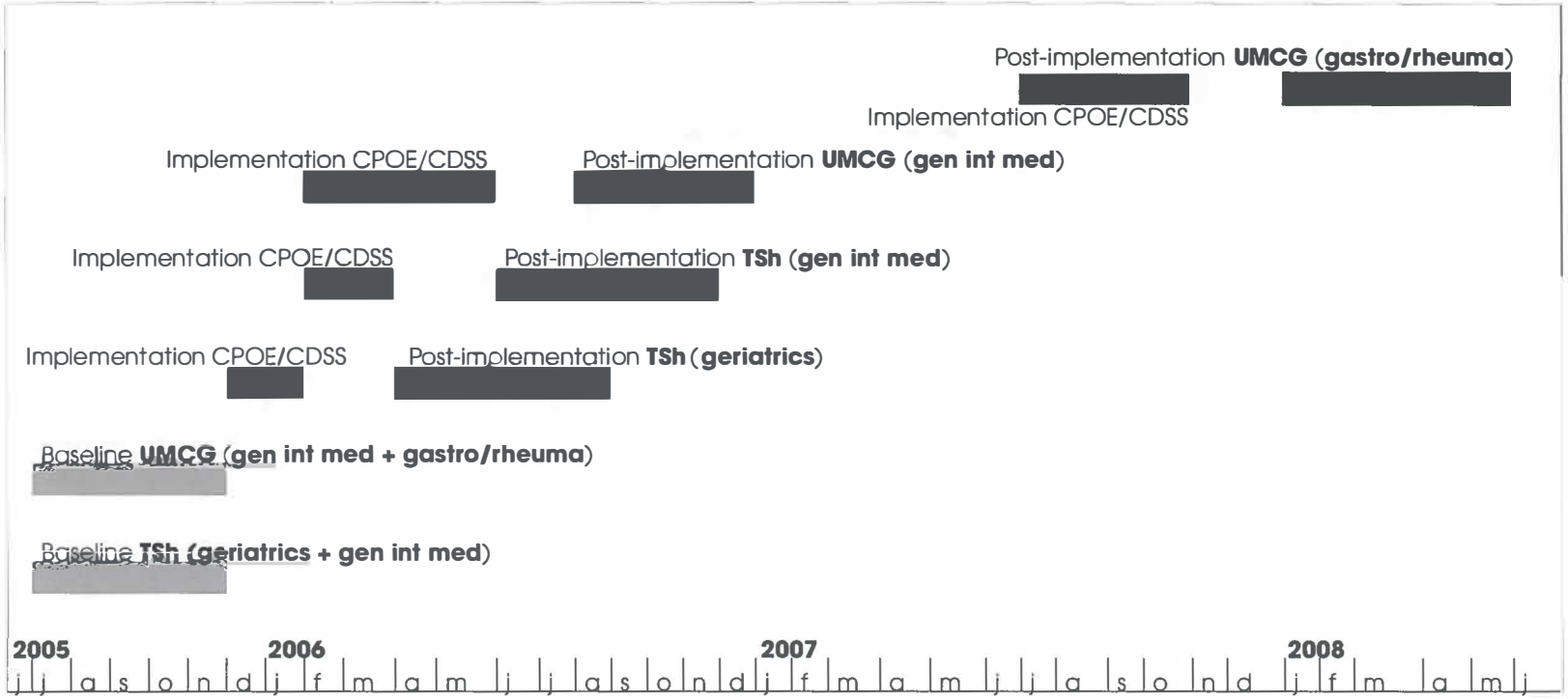


Figure A:study planning

Pre-implementation

In both hospitals, the conventional process of medication ordering during the baseline period was paper-based; physicians prescribed handwritten medication orders on charts and nurses transcribed these medication orders onto the administration charts. From these administration charts nurses read what medication should be administrated to which patients. There was no decision support for the physicians at the moment of prescribing.

During the conventional process, central order entry by the pharmacy was performed in the TweeSteden hospital only. As a result, it was only in the TweeSteden hospital that medication orders were reviewed by pharmacists during the baseline period.

Intervention

The intervention was the introduction of the CPOE/CDSS system. This is a computer-based system by which physicians order medication electronically in a standardised way. In this study, the hospitals used the CPOE/CDSS system only for ordering medication. In the system, medication can be selected from menus in which medication from the local ward stock or from the pharmacy drug database is shown. Physicians are obliged to complete fields with key prescription characteristics (such as frequency and administration route). Moreover, standardised prescriptions and medication protocols (a set of prescriptions belonging to one protocol) can be programmed. In this system, transcription of medication orders by both the nurses and the pharmacy staff was no longer necessary. The CDSS system used was basic: safety alerts were rather straightforward and were only generated in case of drug-drug interactions, overdosing and allergies.[13] This medication control was based on a national drug database for community pharmacies (the Z-index of the Royal Dutch Association of Pharmacists (KNMP)). More advanced CDSS systems currently do exist, which perform more complex functions (e.g., adjustment for renal impairment),[13] but these more advanced CDSS systems are still in an experimental stage in the Netherlands.

Physicians receive safety alerts in real time when prescribing drugs that, for example, interact with already prescribed drugs or when the dosage is too high. When an alert is shown, physicians can continue prescribing by accepting the order (while knowing there is a safety issue) or they can cancel the order. The safety alerts for the accepted medication orders are seen by pharmacists who can contact the physicians and nurses if necessary. In both hospitals, different types of CPOE/CDSS systems were in use. The commercially available system used in the University Medical Center Groningen was Medicator® (iSOFT, Leiden, the Netherlands). In this system, only the process of ordering medication is computerised, the process of dispensing and administering the medication is still paper-based. After the medi-

cation orders are entered into the computer, labels are printed out, which nurses then stick onto the administration charts. This is in contrast to the partly homegrown system used in the TweeSteden hospital in Tilburg, Theriak® (Theriak evf, Tilburg, the Netherlands), a system in which the process of patient identification and medication administration is also automated (i.e., through a closed loop system) by scanning barcodes on patients' wristbands and barcodes on the packaging of medication. As mentioned before, the CDDS system in both Medicator® and Theriak® can be considered to be quite basic.

Data collection

Prospectively, the following patient data were collected by two research pharmacists: patients' characteristics (sex, age, height, weight, duration of stay in the ward), medical history, diseases (reasons for admission and diagnoses during hospital stay), medication (medication orders (MOs) during hospital stay), laboratory values and adverse events (any untoward medical occurrences during hospital stay, which do not necessarily need to be related to medication use). Data were extracted from the hospital information system, medical charts, and the medication order and administration charts, and, during the post-intervention period, from the CPOE/CDSS system as well. Data from periods before and after the patient's admission period were not included (e.g., outpatient information or data from a stay on a ward other than the one included in this study).

Classification of prescribing and transcribing errors

After collecting the data, the two research pharmacists, in parallel, individually reviewed the medication orders and identified medication errors according to the classification scheme for medication errors developed by the Netherlands Association of Hospital Pharmacists.[14] They were not blinded as to whether they assessed data before or after the introduction of CPOE/CDSS. The two research pharmacists were thoroughly trained in the classification scheme before the data collection. Moreover, in the first period of the study the research pharmacists discussed their findings weekly so as to guarantee that they were using the scheme in the same way. They also individually assessed ten pilot patients and afterwards discussed differences in classification. In this scheme, a distinction was made between prescribing, transcribing, dispensing, administering and "across setting" errors. Because CPOE/CDSS was expected to have the largest effect on the number of prescribing and transcribing errors, only these two types of medication errors were taken into account. Prescribing errors are those errors made in the process of prescribing medication. These errors were subdivided into administrative and procedural errors (errors in readability, patient data, ward and prescriber data, drug name, dosage form and route of administration), dosing errors (errors in strength, frequency, dos-

age, length of therapy and directions for use) and therapeutic errors (drug-drug interactions, contra-indications, incorrect mono-therapy, duplicate therapy, and errors in therapeutic drug monitoring or laboratory monitoring; inappropriate drug choices were not actively assessed and were only taken into account when these were obvious). Transcribing errors are errors that occur in the process of the interpreting, verifying and transcribing of medication orders. Transcribing errors were not subdivided into any sub-categories.

Classification of the severity of medication errors/incidence of pADEs

For the assessment of the severity of the identified prescribing and transcribing errors (including whether a related pADE had occurred), the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) scheme[15] and the simplified Yale algorithm[16] were combined into a new assessment tool.[17] The NCC MERP scheme categorizes MEs into nine categories (A through I) based on the severity of the related patient outcomes. Category A is a category for "circumstances or events that have the potential to cause an error," for example, a drug-drug interaction that seems not to be relevant in a specific patient. In our study, we did not include this kind of circumstance as belonging to MEs. Categories B through D are associated with the absence of a preventable ADE, and Categories E through I are associated with the presence of a pADE (Box 1). In order to define whether an ME was categorised in the first group (B through D) or the second group (E through I), a causality assessment needed to be performed between the ME and an adverse event. Therefore, we adopted the first three items of the Yale algorithm in the new assessment tool (knowledge about the relationship between this drug and the event, influence of other clinical conditions, and the time relationship between drug and event). The causal relationship could be assessed as unlikely (score < 0), possible (score ≥ 0 and ≤ 3), and probable (score $= 4$). When the relationship was possible or probable, the ME was categorized as E, F, G, H or I and was defined as a pADE. When the relationship was unlikely, the ME was categorised as B, C or D, and was not associated with a pADE.

The assessment procedure (on severity of medication errors and incidence of pADEs) was carried out by five pharmacists. After individual assessment by the pharmacists, consensus meetings took place where consensus was reached for all cases of causality, between error and adverse event, as well as for severity of the error. The use of a consensus method was based on our findings in another study in which we showed that agreement between individual assessors was low (kappa in range "fair"), irrespective of their professional background (pharmacists and physicians).[17]

Box 1: NCC MERP scheme

Category	Content
A	Circumstances or events that have the capacity to cause error
B	An error occurred but the error did not reach the patient
C	An error occurred that reached the patient but did not cause patient harm
D	An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm
E	An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention
F	An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalisation
G	An error occurred that may have contributed to or resulted in permanent patient harm
H	An error occurred that required intervention necessary to sustain life
I	An error occurred that may have contributed to or resulted in the patient's death

	No error
	Error no harm (no pADE)
	Error harm (pADE)

Outcomes

The two primary outcome measurements were defined as: 1) percentage of medication orders (MOs) with one or more medication errors (MEs); and 2) percentage of admitted patients with one or more preventable adverse drug events (pADEs).

Data analysis

All data were processed using MS Access 2003. SPSS version 14 (SPSS Inc., Chicago, Illinois) was used for the analysis. For the baseline period and the post-intervention period, the frequencies of the different types of MEs and pADEs were calculated, as well as the percentage of medication orders with one or more MEs and the percentage of patients with one or more pADEs. Segmented linear regression analysis was used to assess level and trend for: 1) the percentage of medication orders with one or more MEs at baseline; and 2) the percentage of patients with one or more pADEs at baseline; and to assess to what extent the intervention changed these levels. Separate analyses were performed for the different types of medication errors.

The data points for the time-series data represent the percentage of medication orders with MEs aggregated per week (i.e., 20 data points before and after the intervention) and the percentage of patients with one or more pADEs aggregated per month (i.e., 5 data points before and after the intervention). MEs were analysed using weeks as data points due to their high incidence, while pADEs were analysed using months as data points. The low incidence of pADEs and the limited number of admissions (<30) per week that was expected would otherwise lead to an unstable baseline. Durbin-Watson statistics and visual inspection of the residuals versus time were used to check for possible autocorrelation (correlation between error terms of consecutive observations). In the case of non-significant trends in pADEs, a more parsimonious statistical analysis of mean pADE rate pre- and post-implementation with a Student t-test was also performed.

Power analysis

The study design met the criteria for a robust ITS, that is, 3 data points pre- and post-intervention, each consisting of at least 30 admissions.[18] If trends in pADEs turned out to be non-significant, a more parsimonious statistical analysis of mean pADE rate pre- and post-intervention with a Student t-test was also performed. To detect an assumed 50% decrease in the primary endpoint of medication orders with one or more medication errors (assuming a baseline prevalence of 10%) with a power of 80% and = 5%, 474 medication orders, counted two times, would be required for the Student's t-test. By the same token, to detect a decrease in the number of pADEs per 100 admissions from 15 to 7.5 (rate ratio < 0.5) resulting from the intervention, a sample of 496 admissions equally distributed over pre- and post-intervention periods achieved 80% power at an 0.05 significance level.

To estimate the level and trend of the percentages of medication orders with one or more MEs, and of the percentages of patients with one or more pADEs before the implementation of CPOE/CDSS, and to estimate the changes in level and trend after the implementation of CPOE/CDSS, the following linear regression model was used [12]:

$Y_\tau = \beta_0 + \beta_1 * \text{time}_\tau + \beta_2 * \text{intervention}_\tau + \beta_3 * \text{time after intervention}_\tau + \varepsilon_\tau$

Y_0 = mean percentage at time is 0 = β_0

β_1 = baseline trend

β_2 = immediate change after intervention

β_3 = change in trend

Results

Five-hundred and ninety-two patients during the baseline period and 603 patients during the post intervention period were included **(Table 1)**. Four patients did not

provide consent and were excluded from the study. The mean age of the patients included in both periods was rather high (± 65 years), which can be explained by the inclusion of a geriatric ward from one hospital in this study. During both periods, the mean number of MOs per hospital stay was 12 (baseline 12.3 ± 7.8, intervention 11.7 ± 8.7).

The mean length of hospital stay for our total study population decreased significantly after the introduction of CPOE/CDSS: 14.6 ± 12.5 days pre-implementation versus 12.1 ± 11.6 days post-implementation.

During the baseline period, 55% of all MOs contained at least one error, whereas during the post-intervention period this was 17% **(Figure 1)**. In the baseline period, 15.5% of admitted patients experienced patient harm (pADE), as opposed to 7.3% after CPOE/CDSS was implemented (post-intervention) **(Figure 1)**.

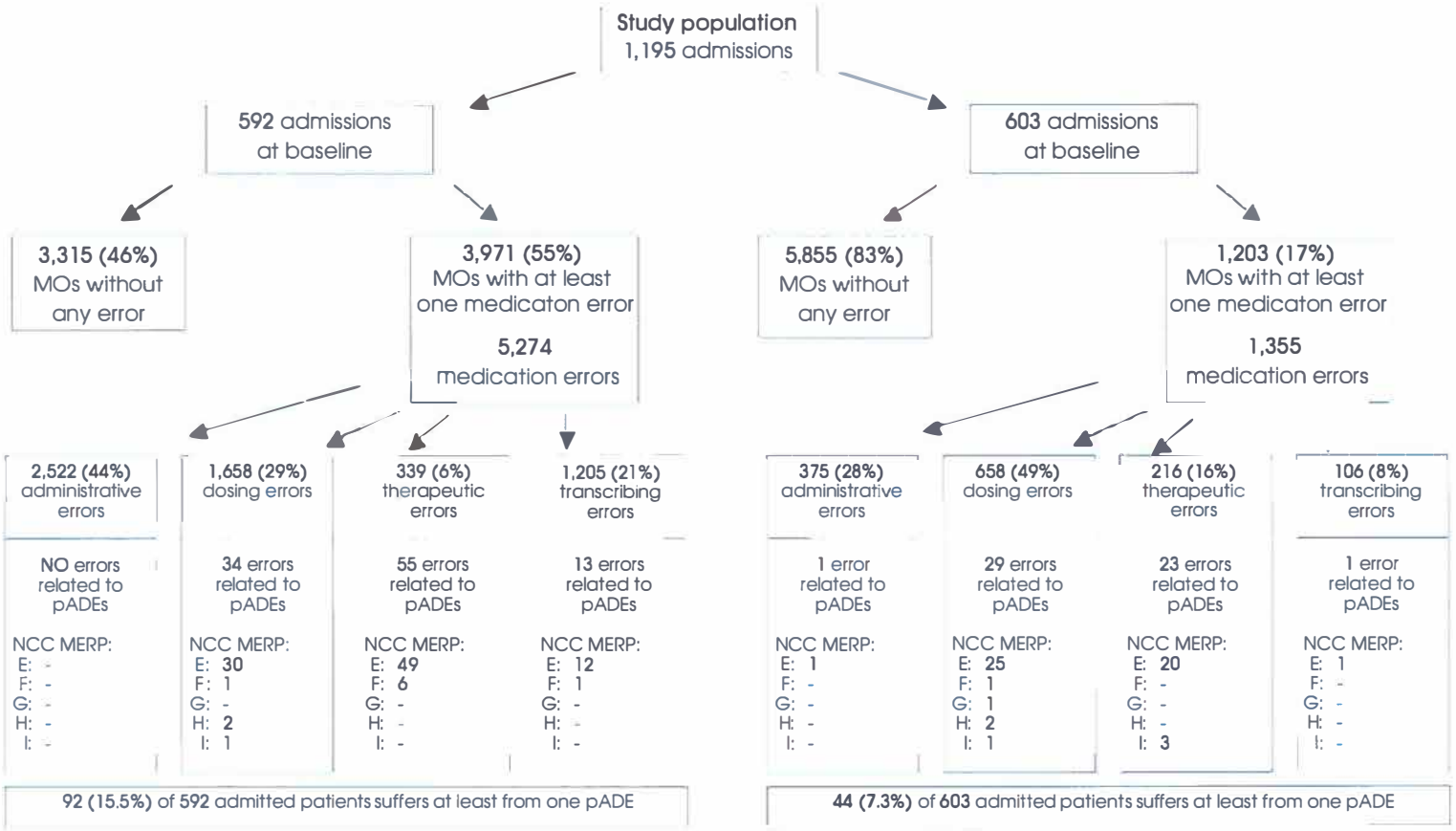
Table 1: Descriptives of the study population

	Study period			Hospital		
	pre	post	p-value*	UMCG	Twee-Steden hospital	p-value*
Age (mean ± SD)	65.5 ± 19.2	65.1 ± 19.1	0.74	58.2 ± 19.1	73.0 ± 16.0	<0.001
Female (%)	54.7	56.6	0.53	55.7	55.6	0.96
MOs per hospital stay (mean ± SD)	12.3 ± 7.8	11.7± 8.7	0.21	11.1± 8.4	13.0 ± 8.1	<0.001
Patients (n)			0.04			*NA***
Internal medicine	251	235		200	286	
Geriatrics	153	135		-	288	
Gastroenterology/ rheumatology	188	233		421	-	
Total	*592*	*603*		*621*	*574*	

* Continues variables are analysed with a t-test and categorical with a Chi-square test.

**NA not appropriate: clearly the distribution per ward was different across the hospital as different wards were included.

Figure 1: Flow chart of study population, medication orders (MOs), medication errors (MEs) and preventable adverse drug events (pADEs)



Effect of CPOE/CDSS

Figures 2 to 4 show the medication error and pADEs patterns during the study period. The introduction of CPOE/CDSS led to a significant immediate absolute reduction of 40.3% (95%CI:-45%; -36%) of medication orders with one or more errors (β2), and a change in trend of -0.92% (95%CI: -1.3%; -0.5%) per week (β3) **(Figure 2)**. The trend of + 0.63% (95% CI: 0.35%; 0.91%) of ME/MO per week that was observed at baseline was remarkable. Similar effect sizes in both trend and immediate change were observed in both hospitals **(Figure 2)**.

The introduction of CPOE/CDSS led to an immediate decrease in level (β2) and trend (β3) for all types of MEs, except for therapeutic errors **(Figure 3)**. The introduction of CPOE/CDSS had the largest impact on the number of administrative and procedural errors (a significant immediate change of -30% (95% CI: -35%; -25%)). The immediate change in dosing and transcribing errors was about the same (-13% respectively -15%). With the introduction of CPOE/CDSS, the incidence of transcribing errors was not reduced to zero as in the University Medical Center Groningen transcribing errors still occurred in the post-intervention period, for example, labels fixed in the wrong place or on the wrong chart, or MOs still prescribed by hand instead of by CPOE/CDSS.

In contrast to the medication errors, the introduction of CPOE/CDSS did not lead to a significant change in level and trend of pADEs **(Figure 4)**. The observed underlying negative trend at baseline -4.0% pADEs per admission per month (95% CI: -7.70%; -0.38%) negated the obvious reduction in pADEs that was observed in the descriptive analysis **(Figure 1)**.

No autocorrelation was detected for any of the outcome parameters presented. Visual inspection of residuals versus time also did not indicate the presence of any autocorrelation.

	Y_0 (95% CI) (mean percentage at time=0; intercept)	β_1 (95% CI) (baseline trend)	β_2 (95% CI) (immediate change)	β_3 (95% CI) (change in trend)
Total**	**47.87*** **(44.58; 51.16)**	**0.63** **(0.35; 0.91)**	**- 40.30** **(- 45.13; - 35.48)**	**- 0.92** **(-1.31; - 0.52)**
TweeSteden hospital	**49.10** **(44.87; 53.34)**	**1.25** **(0.89; 1.61)**	**- 45.19** **(- 51.41; - 38.98)**	**-1.62** **(- 2.13; -1.11)**
UMCG	**42.85** **(39.40; 46.31)**	**0.42** **(0.13; 0.72)**	**- 41.74** **(- 46.81; - 36.67)**	**- 0.56** **(- 0.98; -0.14)**

*Significant values are in bold type face

** Total study population = both hospitals combined

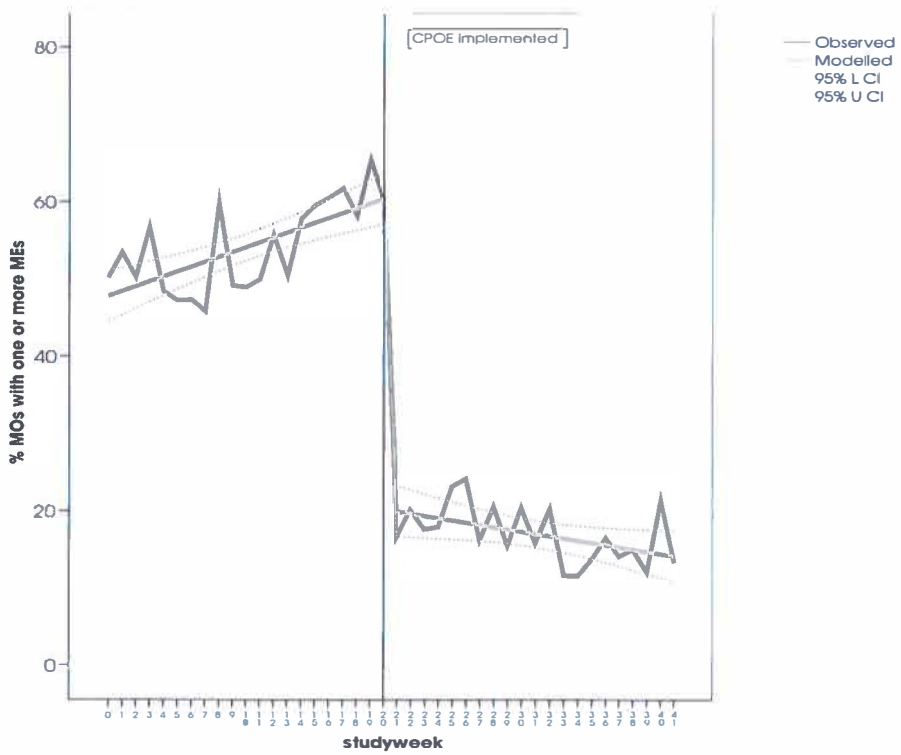


Figure 2: Impact of CPOE/CDSS on percentage of medication orders with one or more medication errors (total study population)

	Y_0 (95% CI) (mean percentage at time=0)	β_1 (95% CI) (baseline trend)	β_2 (95% CI) (immediate change)	β_3 (95% CI) (change in trend)
Administrative errors	**26.34*** **(22.94; 29.74)**	**0.48** **(0.19; 0.77)**	**- 30.37** **(- 35.36; - 25.38)**	**- 0.52** **(- 0.93; - 0.10)**
Dosing errors	**15.69** **(13.21; 18.16)**	**0.38** **(0.17; 0.59)**	**-13.05** **(-16.68; - 9.42)**	**- 0.51** **(-0.81; -0.21)**
Therapeutic errors	**4.71** **(3.71; 5.71)**	- 0.03 (- 0.11; 0.06)	- 0.91 (- 2.37; 0.56)	- 0.01 (- 0.13; 0.11)
Transcribing errors	**10.82** **(8.54; 13.11)**	**0.35** **(0.15; 0.54)**	**-15.30** **(-18.65; - 11.94)**	**- 0.44** **(- 0.72; - 0.16)**

*Significant values are in bold type face

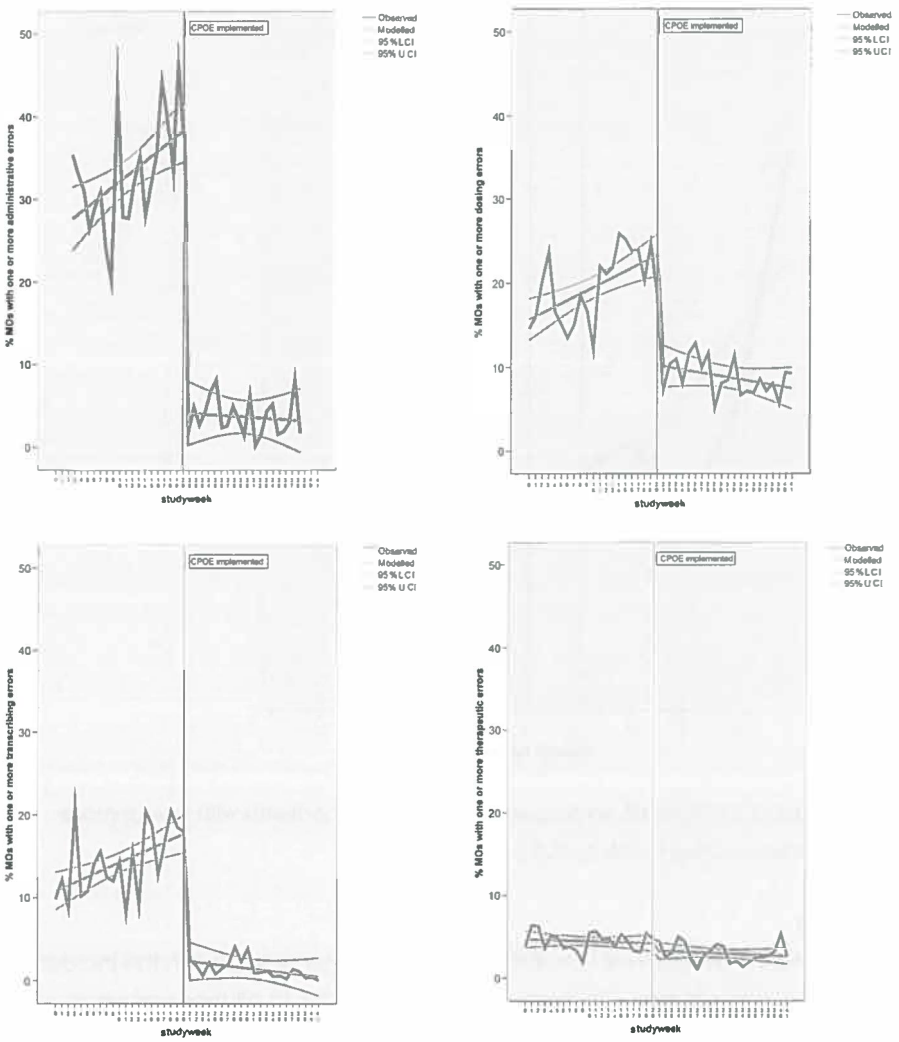


Figure 3: Impact of CPOE/CDSS on percentage of medication orders with one or more subtypes of medication errors. Panels: administrative errors, dosing errors, transcribing errors, therapeutic errors.

Segmented regression analysis for pADEs per month	Y_0 (95% CI) (mean percentage at time=0)	β_1 (95% CI) (baseline trend)	β_2 (95% CI) (immediate change)	β_3 (95% CI) (change in trend)
	28.42* **(16.27; 40.57)**	**- 4.04** **(-7.70; - 0.38)**	- 0.42 (-15.52; 14.68)	3.86 (-1.32; 9.04)

*Significant values are in bold type face

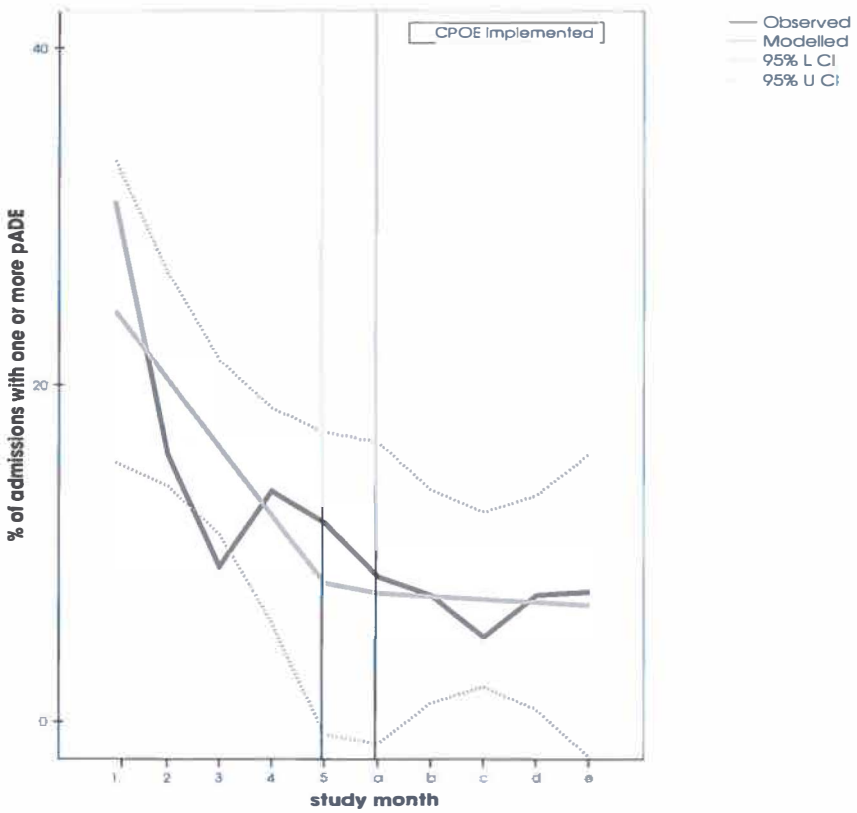


Figure 4: Impact of CPOE/CDSS on percentage of admitted patients with one or more preventable Adverse Drug Events (pADEs).

Discussion

In our study, the introduction of CPOE/CDSS led to a large reduction in the incidence of medication errors in line with findings in earlier studies.[3-9] All types of errors were reduced with the exception of therapeutic errors. However, this substantial reduction in errors was not followed by a significant reduction in the incidence of pADEs.

The lack of effect on pADEs may be explained by the lack of effect on therapeutic errors due to the fact that, as we have demonstrated earlier, this is the very type of medication error most strongly associated with an increased risk of pADEs.[19] Another reason for not finding an effect may be that the CDSS in both hospitals was basic: only in case of overdosing, drug-drug interactions and allergies were alerts generated. To prevent other types of therapeutic errors, more advanced decision-making support would be needed such as, for example, adaptive dose support for patients with clinical chemical parameters that are outside the normal range (e.g., renally excreted medication in patients with renal failure), support when drugs are contraindicated (e.g., in case of the frail elderly) or support for drug choice by linking the system to formularies and disease guidelines that could lead to more optimal pharmacotherapy. A further reason could lie in the inappropriateness of the CDSS in respect to the clinical setting, since the CDSS is based on a national drug database for community pharmacies and not for hospital pharmacies. The standard drug safety alerts that are generated may not always be relevant for the particular hospital setting, for example, an alert for the combination of an ACE-inhibitor and a diuretic that gives rise to a risk of orthostatic hypotension or an alert for a high dose of Furosemide, both very commonly found in the hospital. This may lead to an overload of irrelevant alerts and may cause alert fatigue.[20] One undesirable effect is that physicians not only override irrelevant alerts but also relevant ones. It is possible that other measurements of decision-making support are needed such as clinical pharmacists attending physicians meetings[21] at the medical ward or more intensive education in prescribing skills for junior physicians.[22, 23] On average, fewer patients experienced a pADE in the post-intervention period than in the baseline period (a reduction approximately by half). However, because of the underlying negative trend at baseline, this decrease cannot be attributed to the introduction of CPOE/CDSS. In four recent reviews of the effect of CPOE/CDSS on medication safety, only a few studies evaluated the impact on pADEs or ADEs; this is possibly due to the labor-intensive way the data needed to determine (p)ADEs must be collected and assessed.[3, 7, 8] The evidence from these studies was inconclusive due to the fact that only half of the studies showed any significant effect on (p)ADEs and those studies that did show an impact primarily used a pre/post analysis.[9, 24-26] Our ITS study design with segmented linear regression analysis was more robust because it evaluated the longitudinal effect of an intervention and controlled for trends appearing in the outcome.[12] Thus, differences in the findings between our study and other studies may be explained by the study design chosen and by the data analysis. Although there was no effect on the incidence of pADEs and therapeutic errors, it should be emphasized that the decrease in medication errors in the post-intervention period is likely to contribute to a decreased risk of preventable harm, because medication errors can be considered as proc-

ess measurements, while pADEs are patient outcome measurements.

With respect to the other types of errors, the largest impact was seen on the rate of administrative and procedural errors due to an improvement in readability and due to the fact that key characteristics of a prescription had to be filled in (required fields), which led to more complete medication orders. Although these types of errors do not frequently lead to patient harm,[19] we would argue that it is worthwhile preventing them; when nurses and pharmacy technicians must correct these errors, a substantial amount of valuable time is wasted, which could be better spent on primary patient care. In hospitals with paper-based systems that do not include nurse transcription – a potential source of MEs – the introduction of CPOE/CDSS might lead to a less impressive reduction in MEs. The same may be the case for hospitals that do include pharmacy review in their paper-based systems, which might lead to a lower number of MEs in the baseline than hospitals that have no pharmacy review. In our study the TweeSteden hospital made use of pharmacy review. The similar reduction in MEs found in both hospitals would indicate that pharmacy review in itself does not explain the observed reduction. In the baseline, probably other factors might be as or more important than the presence of this kind of pharmacy review, such as the illegibility and incompleteness of MOs.

The significant upward trend observed in MOs with one or more MEs in the baseline period is surprising. This might well be an artifact stemming from a learning effect for both observers in terms of detecting medication errors. When they were assessing data, the observers were not blinded, neither before nor after the introduction of CPOE/CDSS. It was not feasible, in view of the time constraints, to begin to classify errors only after all data (pre- and post-CPOE/CDSS) had been collected, and therefore we could not blind our data. This is thus one limitation of our study. At the start of the study, the observers individually assessed ten pilot patients and then discussed differences in classification. Despite this pilot period and the use of a strict classification scheme, interpretation of medication errors is subjective and a learning curve cannot be excluded. Another explanation could be that, due to the limited number of data points, the baseline was unstable. Although we have adequately fulfilled the Cochrane criteria of 3 data points before and after the intervention,[18] longer time periods and more data points may well result in a more stable and reliable baseline. One-year data collection before and after CPOE implementation would facilitate a correction for seasonality. However, there is no evidence that pADEs are subject to seasonal influences. Longer data collection was not feasible in our case because of the labor-intensive assessment of pADEs, along with financial constraints.

The delay in implementation on the gastroenterology/rheumatology ward was due to management issues and strategic interests. The eventual implementation process on this ward took as long as on the other ward in the University Medi-

cal Center Groningen (seventeen weeks). As on the other wards, data collection started eight weeks after finishing the implementation process. In another study, we concluded that physicians and nurses were positive about the way CPOE/CDSS was introduced as well as about the system itself.[27] In addition, the CPOE/CDSS users on the gastroenterology/rheumatology ward were also satisfied and did not show any resistance to the system. These findings suggest that the delay would not have had any effect on the results of CPOE/CDSS on MEs and pADEs.

One strength of our study is that we evaluated the impact of CPOE/CDSS in two different types of hospitals with one home-grown and one commercial package. Although these circumstances are considered potential sources of bias, similar effects for medication errors were demonstrated even despite different baseline rates. This emphasises the robustness of our study findings and implies that our results could be applicable to a wider range of settings than those of studies simply evaluating one type of CPOE system in a single hospital.

Our study was performed in adult-based general medical wards, and findings should not be extrapolated to special-care settings such as intensive care wards. Future research may clarify the effect of CPOE/CDSS in these settings. Since investigating the effect of CPOE/CDSS on the readmission rate would have been interesting, future research is also needed into this effect.

Conclusion

Based on our findings it can be concluded that CPOE with basic CDSS decreased medication errors and thus possibly might contribute to a decreased risk of preventable harm. However, we were not able to confirm any effect on actual patient harm. Implementing a CPOE with basic CDSS is simply not enough to prevent pADEs in a general internal medicine/geriatric setting. More effort is needed, such as more advanced CDSS or other forms of clinical decision support.

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References

(1) *To Err is Human: Building a Safer Health System. Washington, DC: National Academy Press; 1999.*

(2) *Kaushal R, Bates DW. Information technology and medication safety: what is the benefit? Qual Saf Health Care 2002 September;11(3):261-5.*

(3) *Wolfstadt JI, Gurwitz JH, Field TS et al. The effect of computerized physician order entry with clinical decision support on the rates of adverse drug events: a systematic review. J Gen Intern Med 2008 April;23(4):451-8.*

(4) *Chaudhry B, Wang J, Wu S et al. Systematic review: impact of health information technology on quality, efficiency, and costs of medical care. Ann Intern Med 2006 May 16;144(10):742-52.*

(5) *Bates DW, Leape LL, Cullen DJ et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. JAMA 1998 October 21;280(15):1311-6.*

(6) *Shamliyan TA, Duval S, Du J, Kane RL. Just what the doctor ordered. Review of the evidence of the impact of computerized physician order entry system on medication errors. Health Serv Res 2008 February;43(1 Pt 1):32-53.*

(7) *Eslami S, de Keizer NF, Abu-Hanna A. The impact of computerized physician medication order entry in hospitalized patients--a systematic review. Int J Med Inform 2008 June;77(6):365-76.*

(8) *Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. Arch Intern Med 2003 June 23;163(12):1409-16.*

(9) *Ammenwerth E, Schnell-Inderst P, Machan C, Siebert U. The Effect of Electronic Prescribing on Medication Errors and Adverse Drug Events: A Systematic Review. J Am Med Inform Assoc 2008 September;15(5):585-600.*

(10) *Koppel R, Metlay JP, Cohen A et al. Role of computerized physician order entry systems in facilitating medication errors. JAMA 2005 March 9;293(10):1197-203.*

(11) *Han YY, Carcillo JA, Venkataraman ST et al. Unexpected increased mortality after implementation of a commercially sold computerized physician order entry system. Pediatrics 2005 December;116(6):1506-12.*

(12) *Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther 2002 August;27(4):299-309.*

(13) *Kuperman GJ, Bobb A, Payne TH et al. Medication-related clinical decision support in computerized provider order entry systems: a review. J Am Med Inform Assoc 2007 January;14(1):29-40.*

(14) Bemt van den PMLA, Egberts ACG. Drug-related problems: definitions and classifications. EJHP 2006;12((suppl.)):10-2.

(15) National Coordinating Council For Medication Error Reporting and Prevention (NCCMERP). NCC MERP index for categorizing medication errors. http://www.nccmerp.org/ (accessed September 2008)

(16) Kramer MS, Leventhal JM, Hutchinson TA, Feinstein AR. An Algorithm for the Operational Assessment of Adverse Drug Reactions. JAMA 1979;242:623-32.

(17) van Doormaal JE, Mol PG, van den Bemt PM et al. Reliability of the assessment of preventable adverse drug events in daily clinical practice. Pharmacoepidemiol Drug Saf 2008 July;;17(7):645-54.

(18) The Cochrane Effective Practice and Organisation of Care Group (EPOC). http://www.epoc.cochrane.org/Files/Website/Reviewer%20Resources/inttime.pdf (accessed September 2008)

(19) van Doormaal JE, van den Bemt PM, Mol PG et al. Medication errors: the impact of prescribing and transcribing errors on preventable harm in hospitalised patients. Qual Saf Health Care 2009 February;;18(1):22-7.

(20) van der Sijs H, Aarts J, Vulto A, Berg M. Overriding of drug safety alerts in computerized physician order entry. J Am Med Inform Assoc 2006 March;13(2):138-47.

(21) Kaboli PJ, Hoth AB, McClimon BJ, Schnipper JL. Clinical pharmacists and inpatient medical care: a systematic review. Arch Intern Med 2006 May 8;166(9):955-64.

(22) Heaton A, Webb DJ, Maxwell SR. Undergraduate preparation for prescribing: the views of 2413 UK medical students and recent graduates. Br J Clin Pharmacol 2008 July;66(1):128-34.

(23) Coombes ID, Mitchell CA, Stowasser DA. Safe medication practice: attitudes of medical students about to begin their intern year. Med Educ 2008 April;42(4):427-31.

(24) Upperman JS, Staley P, Friend K et al. The impact of hospitalwide computerized physician order entry on medical errors in a pediatric hospital. J Pediatr Surg 2005 January;40(1):57-9.

(25) Evans RS, Pestotnik SL, Classen DC, Horn SD, Bass SB, Burke JP. Preventing adverse drug events in hospitalized patients. Ann Pharmacother 1994 April;28(4):523-7.

(26) Evans RS, Pestotnik SL, Classen DC et al. A computer-assisted management program for antibiotics and other antiinfective agents. N Engl J Med 1998 January 22;338(4):232-8.

(27) van Doormaal JE, Mol PGM, Zaal RJ, van den Bemt PMLA, Kosterink JGW, Vermeulen KM, et al. Computerised Physician Order Entry (CPOE) system: expectations and experiences of users. Accepted for publication in the Journal of Evaluation in Clinical Practice.

Chapter 6

Comparison of methods to identify patients at risk for medication related harm

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Abstract

Background:
With the introduction of Computerised Physician Order Entry (CPOE) in routine hospital care much effort is put in refining Clinical Decision Support Systems (CDSS) to identify patients at risk of preventable medication related harm.

Objectives:
To identify to what extent patients at risk for medication related harm as identified by basic CDSS and clinical rules (advanced CDSS) actually need a change in medication as indicated by medication review.

Methods:
In this cross-sectional study a change needed in medication was indicated by dosing and therapeutic errors which were identified through manual medication review of 313 patients admitted during 5 months to an internal medicine ward by a trained pharmacist. In a test setting the medication orders (MOs) of these patients were entered into a CPOE with basic CDSS and generated safety alerts were collected. Secondly a set of 16 clinical rules was applied to the patient and prescribing data in MS Access 2003. Overlap between CDSS and clinical rules was determined.

Results:
Medication review identified 2171 medication errors of which 57 were classified as an overdose and 143 as therapeutic errors (e.g. drug-drug interactions or contra-indication). CDSS identified 297 overdoses, with sensitivity 0.32, specificity 0.92 and positive predictive value (PPV) 0.06; and 365 drug-drug interactions, with sensitivity 0.96, specificity 0.91 and PPV 0.12. The clinical rules identified 78 (39%) of the 200 overdoses and therapeutic errors at which they were targeted. In 72 (23 %) of 313 alerts generated a change of medication was actually indicated. When combined CDSS and rules identified 131 (66%) of the 200 errors.

Conclusions:
Clinical rules combined with basic CDSS hold promise for routine use to identify patients at risk of preventable harm, but still need fine tuning since for a considerable number of alerts no subsequent change in medication is needed.

Introduction

A substantial part of the hospitalised patients experience medication related harm that is preventable, for example due to incorrect dosing, contra-indicated drug choice or drug-drug interactions.[1-4] To improve the situation, much effort is put in different strategies to prevent such problems. One strategy is structured reviewing of patients' medication (medication review) by physicians or pharmacists to identify patients with medication errors (MEs) that may lead to harm. A limitation of this system is the retrospective character which implies a late intervention. Moreover this approach is very labour intensive since all medication of all patients has to be systematically reviewed. The advantage is that the complete clinical situation of the patient is taken into account when identifying problems, and only those problems are identified where action, a change of medication, is actually needed. A less labour intensive strategy is the use of computerised trigger systems. These systems can identify patients at risk for medication related harm (adverse drug events, ADEs) using either data on the prescribed medication only or the combination of medication with certain patient characteristics or clinical laboratory values.[5-9] An example of such systems is the Clinical Decision Support system (CDSS) within Computerised Physician Order Entry (CPOE) systems.[10] In the Netherlands, the CDSS integrated in most types of CPOE systems is basic; only in case of drug overdoses and drug-drug interactions alerts are generated. For successful identification of high risk patients more is needed, such as identification of patients at risk of dosing problems in case of clinical deviating chemistry parameters or determined blood drug concentrations or of the need to change a specific medicine (the appropriate antibiotic) for a specific disease.[11, 12] Currently some hospitals in the Netherlands are developing in addition to the basic CDSS more advanced support by creating defined clinical rules - basically computerised algorithms that look for specific medication orders, patient characteristics and/or laboratory values that identify patients at risk for suboptimal therapy but also for medication harm.[13] The advantage of such computerised systems is clearly that they limit labour input dramatically. Such systems should be sensitive enough to identify patients at risk, but also specific enough to generate clinically relevant alerts in order to prevent alert fatigue.

In this study we compare two computerised systems (a basic CDSS within a CPOE and the use of clinical rules) with medication review to answer the question to what extent patients at risk for medication related harm as identified by the two computerised systems actually have a medication error as identified by the medication review method.

Methods

This study is conducted in the framework of a study on the effect of a computerised Physician Order Entry system on Medication Safety (POEMS study).

Setting and study population

This study was performed in two general internal medicine wards and one gastroenterology/rheumatology ward in the UMCG. All patients admitted for more than 24 hours to these wards were included (313 patients). A waiver of the Medical Ethical Committee was obtained for this study, as the study fell within the boundaries of normal hospital routine of quality improvement. Patients received information about the study and they could object to inclusion. During the study period the system of medication ordering was the conventional paper based system; physicians wrote their medication orders on paper charts and nurses transcribed these orders on administration charts.

Study design and data collection

Our study had a cross-sectional design. The following patient data were collected in daily ward visits: patients' characteristics (sex, age, length, weight, duration of stay on ward), medical history, diseases (reasons for admission and diagnoses during hospital stay), medication (medication orders (MOs) during hospital stay), laboratory values and adverse events (any untoward medical occurrences during hospital stay, which do not necessarily need to be related to medication use). Data were extracted from the hospital information system, medical charts, medication orders and administration charts.

Methods to identify medication errors or patients at risk

- Medication review method to identify medication errors

In the framework of the POEMS study all MOs were reviewed by a trained research pharmacist (JvD) with regard to the presence of medication errors (MEs) according to the classification scheme of the Netherlands Association of Hospital Pharmacists[14] and considering the complete clinical situation of the patient. The MEs were classified regarding administrative and procedural errors (e.g. errors on readability or missing route of administration), dosing errors (e.g. drug overdoses or incorrect length of therapy), therapeutic errors (e.g. drug-drug interactions or contra-indications) and transcribing errors (MOs which are wrongly transcribed on the administration chart).

In this study we included only dosing and therapeutic errors. These errors if not corrected have a high probability to lead to medication related harm[2, 15-18] and are therefore the prime target of clinical decision support systems.

- CDSS within CPOE system

All MOs were manually entered into a test environment of the CPOE/CDSS system, the commercially available Medicator® (iSOFT, Leiden, the Netherlands). The CDSS system of Medicator® is basic; safety alerts are generated only in case of overdoses or drug-drug interactions.[19] These safety alerts are shown to physicians during the prescribing phase. This medication surveillance is based on a national drug database for community pharmacies (the 'G-standard', Z-index BV, The Hague, the Netherlands).

After entering the MOs into the system, all generated safety alerts were collected and both MOs and alerts were registered in a SPSS database (version 14). Per MO a variable was included indicating the absence or presence and type of safety alert (overdose or drug-drug interaction).

- Computer based clinical rules

Leiden University Medical Center (LUMC) has developed a computerised alert system that uses clinical rules to detect patients with a potential adverse drug event or are at risk for an adverse drug event. The system uses combined data from the CPOE, the hospital information system (e.g. laboratory values) and the national drug information database ('G-Standard') to detect potential patients at risk. The detection is based on defined algorithms, the so called clinical rules. Currently, more than 100 clinical rules are defined and agreed on by a multidisciplinary team, including a pharmacist, a hospital pharmacist, an internal medicine specialist and a clinical pharmacologist. The clinical rules and the computer system are tested and validated. A pilot study was performed in the LUMC to compare this new computerised alert system with the conventional medication surveillance in the CPOE/CDSS to assess its additional value. This prospective pilot study was conducted on a general internal medicine ward during 6 months. Twenty different clinical rules led to an alert in the small patient population admitted to this ward.

In our current study comparing this computerised approach to the patients identified as having a medication error, we excluded the four rules that were not defined as a medication error in the medication review, resulting in a set of 16 rules (see **table 4**). For each clinical rule a query was designed in MS Access 2003. These queries were applied to the patient data to assess how many patients were triggered by the clinical rules.

Analysis

Data were processed with MS Access 2003. SPSS version 14 was used for the analysis. For the total number of MOs the safety alerts generated by CDSS were compared to the errors on overdoses or drug-drug interactions detected by the medication review method. The overlap between the CDSS and the medication review

method was analysed by calculating the sensitivity, specificity and positive predictive value (PPV) for both the support on overdoses and the support on drug-drug interactions. The overlap between the clinical rules and the medication review method was analysed for the patients identified by the clinical rules as being at risk and limited to patients with an identical medication error. Therefore sensitivity and specificity were not calculated, since patients without an alert and with a related medication error were not included. The overlap was manually reviewed and subsequently analysed by calculating the percentage of patients that were identified to be at risk in both systems. For the medication review method only those patients with an error that corresponded to the related clinical rule were identified.

Results

In the ***medication review method*** 622 dosing errors and 143 therapeutic errors were found. The different types of dosing and therapeutic errors are shown in **table** 1. The subtypes 'overdose' and 'drug-drug interaction' were detected 57 respectively 46 times.

Table 1: Frequency of different types of errors - medication review method

Type of medication error	*Number (n)*
Dosing	
Strength	205
Dosing frequency	199
Overdose	**57**
No maximum for 'as needed'	99
Underdose	35
Duration of therapy	17
Directions for use	10
Total	622
Therapeutic	
Indication	19
Contraindication	19
Drug-drug interaction	**46**
Improper monotherapy	18
(Pseudo)double medication	40
Therapeutic monitoring	1
Total	143

In total 297 safety alerts on overdoses were generated by the ***basic CDSS within the CPOE***. The PPV of this type of support was low (0.06), i.e. few of the generated safety alerts were indeed indicated as actual overdoses by the medication review method. The sensitivity of the support was higher but still not optimal (0.32). **(Table 2)**

Table 2: basic CDSS system within the CPOE system- support on overdoses

		Overdose in medication review (reference)		*Medication orders (n)*
		Yes	*No*	
Safety alerts on overdoses	*Yes*	18	279	*297*
	No	39	3224	*3263*
Total		57	3503	*3560*

Sensitivity *0.32*

Specificity *0.92*

PPV *0.06*

In total 365 safety alerts on drug-drug interaction were generated by the **basic CDSS within the CPOE.** Although the PPV was low (0.12), the sensitivity of the support was high (0.96). **(Table 3)** Almost all drug-drug interactions provide an alert by the system but the majority of the problems are not considered as medication errors in the medication review method when other patient data are taken into account.

Table 3: basic CDSS system within the CPOE system - support on drug-drug interactions

		Drug-drug interactions in medication review (reference)		*Medication orders (n)*
		Yes	*No*	
Safety alerts on drug-drug interactions	*Yes*	44	321	*365*
	No	2	3193	*3195*
Total		46	3514	*3560*

Sensitivity *0.96*

Specificity *0.91*

PPV *0.12*

The set of sixteen ***clinical rules*** triggered in total 313 patients. In 72 (23%) of these patients the medication review method also identified one or more related MEs **(table 4)**. This were in total 78 MEs (data not shown). Thus 23% of the patients triggered to be at risk therefore actually need a change in medication or other kind of action to prevent an ME. For two rules the percentage of patients actually requiring a change in medication could not be determined because no patients were triggered and for seven clinical rules this percentage was zero. For the other clinical rules this percentage varies between 10 and 58 **(table 4)**. The percentage was highest for the rule 'use of an opioid and no prescription for a laxative' (58%). The main focus of the rest of the set clinical rules is to prevent potential therapeutic errors and potential overdoses in relation to declined renal function. In the medication review method 143 therapeutic errors and 57 overdoses were found **(table 1)**. The set of sixteen clinical rules identified 78 MEs 39% of these 143 therapeutic errors and 57 overdoses found in the medication review method. Together CDSS and the clinical rules detect 18 overdoses + 44 drug-drug interactions + 69 clinical rule alerts (excluding rule 14 that signalled patients that were already detected in basic CDSS) = 131 (66%) of the 200 overdose and prescribing errors found in the medication review method.

In **box 1** some examples are given why patients triggered to be at risk of medication harm with the basic CDSS within the CPOE or the clinical rules were not considered to have medication errors according to the medication review method.

Table 4: Selected set of sixteen clinical rules

	Number of patients triggered by **clinical rule**	Number of patients with a corresponding error in **medication review (%)**
1. Clearance < 50 mL/min or serum creatinine > 150 µmol/L	129	23 (18)
2. Serum creatinine Increase of > 50 µmol/L or of > 50%	37	11(30)
3. Use of Cefuroxime and clearance < 50 mL/min	7	0 (0)
4. Use of Ceftazidime and clearance of < 100 mL/min	2	0 (0)
5. Use of Ciprofloxacin and clearance of < 25 mL/min	11	2 (18)
6. Use of Ranitidine and clearance of < 50 mL/min	5	1 (20)
7. Use of Cetirizine and clearance of < 10 mL/min	0	0 (-)
8. Use of Sulphonamides urea derivate and clearance of < 10 mL/min	0	0 (-)
9. Gabapentine of pregabaline and clearance of < 50 ml/min	1	0 (0)
10. Use of Digoxin > 0.0625 mg and • age > 70 yrs or • clearance < 50 ml/min or • low level of K or • unknown level of K	14	0 (0)
11. A serum level of aminoglycoside or Vancomycin	3	0 (0)
12. Use of opioid and no prescription for laxative	45	26 (58)
13. Use of Ciprofloxacin or Norfloxacin and use of antiepileptic	2	0 (0)
14. Use of Bisphosphonate and drug which has an effect on the absorption	29	3 (10)
15. Use of Iron and a drug which forms a complex with Iron	11	6 (55)
16. Use of Azathioprine (check dose)	17	0 (0)
TOTAL	313	72 (23)

Box 1 Signal with CPOE/CDSS or clinical rule but no medication error in medication review

Signal	Reasoning
CPOE/CDSS overdose e.g.: Furosemide IV 40 mg OD Amoxicillin IV 1 g QID Omeprazole IV 40 mg BID	All these doses are well accepted in a clinical setting in a more severely ill patient population and deviate from the maximum recommended doses in a community setting for which the medication control database has been developed.
CPOE/CDSS drug-drug interaction, e.g.: NSAIDs and prednisolone	Due to the increased risk of gastro-intestinal irritation this combination should be avoided or gastric protection should be given. In case that a proton pump inhibitor was administered simultaneously this interaction was not considered an ME as the appropriate action had been taken.
Clinical rules e.g. number: 12. Use of opioid and no prescription for laxative 10. Digoxin rule **(table 4)** 1. to 10. impaired renal function and potential for drug overdose	12. Patient receives only single dose of opiate (e.g. morphine IV stat), or has diarrhea when the signal is generated 10. e.g. patient has low potassium levels but gets potassium suppletion 1. to 10. Dose has been adapted in line with recommendations of the level of renal impairment

Discussion

In a considerable number of patients at risk for medication related harm identified by both computerised systems, the basic CDSS within a CPOE and the clinical rules, no medication error was found by the medication review method. Nevertheless, sensitivity and specificity of the basic CDSS to signal drug-drug interactions were good despite the low PPV. This study also shows that with a small set of clinical rules a fair proportion (39%) of medication errors detected with the medication review can be prevented and when the two systems are combined this increases to 66%.

CPOE/CDSS

In their review on medication related clinical decision support in CPOE systems Kuperman et al.[20] showed that CDSS can be divided into two stages, i.e. basic support -which covers the basic principles of support such as drug-drug interaction checking and basic dosing guidance- and more advanced support – which covers in addition more complex support such as dosing support for susceptible patients or guidance for medication-related laboratory testing. The CDSS in Medicator® can be considered as basic and the set of clinical rules as a form of advanced decision support that can be used on top of CDSS. Because both CDSS and the set of clinical rules focus only on part of medication related problems, they should be further developed in the future to cover more potential problems. However, first it is important to guarantee that the current support is optimised. To our knowledge our study is the first that looks into the capability of CDSS in CPOE systems to identify patients truly in need of a change of medication to prevent potential harm, i.e. the sensitivity and PPV to identify medication errors.

Our findings show that CPOE/CDSS generates many less relevant signals (PPV ≤ 0.12) where the reported overdose or drug-drug interaction does not need a subsequent change in medication. Nevertheless CPOE/CDSS misses a considerable number of overdoses (sensitivity = 0.32) identified through medication review. One reason for this low sensitivity may be the lack of dosing support for susceptible patients (patients with renal failure, geriatric patients or children), one of the features of more advanced support systems such as the clinical rules. The reason for a low PPV might be that the alerts are based on a database for community pharmacies (the 'G-standard') instead of for hospital pharmacies. This leads to a number of irrelevant alerts for the hospital setting, such as alerts for an overdose that is perfectly acceptable in hospital but not in ambulatory care. To increase the PPV, this database should be further adapted to the hospital setting to prevent alert fatigue among hospital physicians.[21]

Despite the high sensitivity and specificity of the drug-drug interaction alerts, many signals were generated that did not need a subsequent change in medication (low PPV). The challenge is thus to strike an optimal balance between the number of alerts that do not need follow up and the sensitivity to find serious drug-drug interactions or overdoses. The most relevant determinant for including an alert should be the severity of the consequences of the overdose or drug-drug interaction. For example, in case of the drug-drug interactions with clozapine or methotrexate that could lead to myelosuppression and agranulocytosis, a high sensitivity is in this case more important than a high PPV. Obviously when there are less severe consequences, such as the combination of calciumcarbonate and bisphosphonate that may lead to a decrease in the absorption of bisphosphonate, the need for a high PPV becomes more important. To improve the PPV in the latter case, the alert

could be refined by including the time of administering in order to generate only alerts when both drugs are administered at the same time. In short, it is important to assess the different alerts on clinical relevance and fine tune them to create an optimal number of signals.[22] These considerations have led to the development of the clinical rules discussed below and various approaches are currently undertaken in developing better clinical decision support systems to be used in addition to the basic CDSS.

Clinical rules

In this study we tested a small set of clinical rules. Overall the clinical rules mean an improvement in identifying patients at risk in need of an actual change in medication. Whereas only up to 12% of the alerts generated by CPOE/CDSS needed a subsequent change in medication this was 23% of the alerts generated by the clinical rules. When the two are combined two-thirds of the medication errors are identified.

Like the basic CDSS, the clinical rules generated signals that did not need a subsequent change in medication. Also with clinical rules the challenge is thus to strike an optimal balance between the number of alerts that need action or warning for potential risk full situations and alerts that do not need follow up. For example the rules 1-9 regarding the use of medication and a declined renal function **(table 4)** can be made more efficient by incorporating a cut off dose below which no action and thus no alert is needed. Other rules, for example 'the use of an opioid receptor agonist and no prescription of a laxative', are already quite efficient in selecting risk situations but can be made more efficient in adding a exclusion regarding the single dose.

Other trigger tools have been developed with the same intention.[5-8, 23-25] Some of these studies compared their tools to other methods to identify medication errors and adverse drug events such as manual review or voluntary reports.[5-7] Others only verified the generated signals on the presence of medication errors or adverse drug events.[6, 8, 25] Although these studies are positive in their conclusions, they all showed that additional information usually has to be collected about the individual patient to know whether medication actually has to be changed.

The advantage of these computerised CDSS and trigger tools when combined is clearly that they are much less labour-intensive. Their effectiveness in daily practice will also be affected by the efficiency in triggering patients at risk that are actually in need of change of medication. If not they run the risk of alert fatigue, i.e. generating alerts that need no clinical or medication action.

Our study was limited by the fact that the medication review method was performed by only one investigator. However a strict classification scheme was used to identify medication errors. This scheme distinguishes precisely different subtypes of medication errors and did not allow much room for difference in interpretation. The investigator was extensively trained in using this classification scheme. Another limitation of this study was that the set of clinical rules studied was small (only sixteen rules). The majority of these rules focused on support for patients with renal failure and covered thus a small therapeutic area. In other studies often more diverse rules were assessed which gives further information about the effect of computerised rules in the field of different therapeutic areas.[7, 25, 26]

Conclusions

We may conclude that our basic CDSS within a CPOE and the clinical rules are useful early strategies to prevent medication related harm. They can be the first step to more advanced decision support. These computerised systems will be even more useful in daily practice when they are further fine tuned to decrease the number of alerts that need no clinical action.

References

(1) *To Err is Human: Building a Safer Health System. Washington, DC: National Academy Press; 1999.*

(2) *Kanjanarat P, Winterstein AG, Johns TE, Hatton RC, Gonzalez-Rothi R, Segal R. Nature of preventable adverse drug events in hospitals: a literature review. Am J Health Syst Pharm 2003 September 1;60(17):1750-9.*

(3) *Gurwitz JH, Field TS, Judge J et al. The incidence of adverse drug events in two large academic long-term care facilities. Am J Med 2005 March;118(3):251-8.*

(4) *Dean B, Schachter M, Vincent C, Barber N. Prescribing errors in hospital inpatients: their incidence and clinical significance. Qual Saf Health Care 2002 December;11(4):340-4.*

(5) *Jha AK, Kuperman GJ, Teich JM et al. Identifying adverse drug events: development of a computer-based monitor and comparison with chart review and stimulated voluntary report. J Am Med Inform Assoc 1998 May;5(3):305-14.*

(6) *Seger AC, Jha AK, Bates DW. Adverse drug event detection in a community hospital utilising computerised medication and laboratory data. Drug Saf 2007;30(9):817-24.*

(7) *Field TS, Gurwitz JH, Harrold LR et al. Strategies for detecting adverse drug events among older persons in the ambulatory setting. J Am Med Inform Assoc 2004 November;11(6):492-8.*

(8) Classen DC, Pestotnik SL, Evans RS, Burke JP. Computerized surveillance of adverse drug events in hospital patients. 1991. Qual Saf Health Care 2005 June;14(3):221-5.

(9) Nightingale PG, Adu D, Richards NT, Peters M. Implementation of rules based computerised bedside prescribing and administration: intervention study. BMJ 2000 March 18;320(7237):750-3.

(10) Bates DW. Using information technology to reduce rates of medication errors in hospitals. BMJ 2000 March 18;320(7237):788-91.

(11) Raschke RA, Gollihare B, Wunderlich TA et al. A computer alert system to prevent injury from adverse drug events: development and evaluation in a community teaching hospital. JAMA 1998 October 21;280(15):1317-20.

(12) Peterson JP, Colucci VJ, Schiff SE. Using serum creatinine concentrations to screen for inappropriate dosage of renally eliminated drugs. Am J Hosp Pharm 1991 September;48(9):1962-4.

(13) Rommers MK, Teepe-Twiss IM, Guchelaar HJ. Preventing adverse drug events in hospital practice: an overview. Pharmacoepidemiol Drug Saf 2007 October;16(10):1129-35.

(14) Bemt van den PMLA, Egberts ACG. Drug-related problems: definitions and classifications. EJHP 2006;12((suppl.)):10-2.

(15) Kopp BJ, Erstad BL, Allen ME, Theodorou AA, Priestley G. Medication errors and adverse drug events in an intensive care unit: direct observation approach for detection. Crit Care Med 2006 February;34(2):415-25.

(16) Leape LL, Bates DW, Cullen DJ et al. Systems analysis of adverse drug events. ADE Prevention Study Group. JAMA 1995 July 5;274(1):35-43.

(17) Bates DW, Cullen DJ, Laird N et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. JAMA 1995 July 5;274(1):29-34.

(18) van Doormaal JE, van den Bemt PM, Mol PG et al. Medication errors: the impact of prescribing and transcribing errors on preventable harm in hospitalised patients. Qual Saf Health Care 2009 February;18(1):22-7.

(19) Kalmeijer MD, Holtzer W, van Dongen R, Guchelaar HJ. Implementation of a computerized physician medication order entry system at the Academic Medical Centre in Amsterdam. Pharm World Sci 2003 June;25(3):88-93.

(20) Kuperman GJ, Bobb A, Payne TH et al. Medication-related clinical decision support in computerized provider order entry systems: a review. J Am Med Inform Assoc 2007 January;14(1):29-40.

(21) van der Sijs H, Aarts J, Vulto A, Berg M. Overriding of drug safety alerts in computerized physician order entry. J Am Med Inform Assoc 2006 March;13(2):138-47.

(22) van der Sijs H, Aarts J, van Gelder T, Berg M, Vulto A. Turning off frequently overridden drug alerts: limited opportunities for doing it safely. J Am Med Inform Assoc 2008 July;15(4):439-48.

(23) *Resar RK, Rozich JD, Simmonds T, Haraden CR. A trigger tool to identify adverse events in the intensive care unit. Jt Comm J Qual Patient Saf 2006 October;32(10):585-90.*

(24) *Resar RK, Rozich JD, Classen D. Methodology and rationale for the measurement of harm with trigger tools. Qual Saf Health Care 2003 December;12 Suppl 2:ii39-ii45.*

(25) *Rozich JD, Haraden CR, Resar RK. Adverse drug event trigger tool: a practical methodology for measuring medication related harm. Qual Saf Health Care 2003 June;12(3):194-200.*

(26) *Morimoto T, Gandhi TK, Seger AC, Hsieh TC, Bates DW. Adverse drug events and medication errors: detection and classification methods. Qual Saf Health Care 2004 August;13(4):306-14.*

Chapter 7

Computerised Physician Order Entry (CPOE) system: expectations and experiences of users

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Abstract

Objectives

To explore physicians' and nurses' expectations before and experiences after the implementation of a Computerised Physician Order Entry (CPOE) system in order to give suggestions for future optimisation of the system as well as the implementation process.

Method

On four internal medicine wards of two Dutch hospitals 18 physicians and 42 nurses were interviewed to measure expectations and experiences with the CPOE system. Using semi-structured questionnaires expectations and experiences of physicians and nurses with the CPOE system were measured with statements on a five-point Likert scale (1 = completely disagree, 5 = completely agree). The percentage respondents agreeing (score of 4 or 5) was calculated. Chi-square tests were used to compare the expectations versus experiences of physicians and nurses and to assess the differences between physicians and nurses.

Results

In general, both physicians and nurses were positive about CPOE before and after the implementation of this system. Physicians and nurses did not differ in their views towards CPOE except for the overview of patients' medication use that was not clear according to the nurses. Both professions were satisfied with the implementation process. CPOE could be improved especially with respect to technical aspects (including the medication overview) and decision support on drug-drug interactions.

Conclusion

Overall we conclude that physicians and nurses are positive about CPOE and the process of its implementation and do accept these systems. However, these systems should be further improved to fit into clinical practice.

Introduction

With the introduction of Computerised Physician Order Entry systems (CPOE) in an increasing number of hospitals the electronic way of medication ordering is becoming more common. The shift from a paper-based to a computerised system affects clinical practice.[1] Mainly based on experiences in the USA we know that CPOE has benefits in comparison to a paper-based system; more structured and legible medication orders[2] and clinical decision support during the prescribing phase. These benefits have been shown to contribute to a reduction in the number of medication errors identified in studies that evaluated the impact of CPOE on medication safety.[3-5]

However disadvantages are also known such as rigidity of the system[6], negative effect on the collaboration between physicians and nurses[7, 8] and new types of medication errors introduced by the system.[9] Most studies, however, show that these disadvantages are outweighed by the advantages, leading to increased medication safety. In order to achieve such a positive effect, the system should be successfully implemented taking into account the views, needs and acceptance of the users, i.e. the physicians and nurses.[1, 10] Evaluation of the impact of the system enables improvements and adaptations.[1, 10, 11]

The aim of this study was to explore physicians' and nurses' expectations before and experiences after the implementation of CPOE in order to give suggestions for future optimisation of the system and its use as well as suggestions for the implementation process.

Methods

Setting and design

This survey study was conducted in two medical wards of the 1300-bed University Medical Center Groningen (UMCG) (a general internal medicine and a gastroenterology/rheumatology ward) and in two medical wards of the 600-bed teaching hospital 'TweeSteden' in Tilburg and Waalwijk (TSh) (a geriatric and a general internal medicine ward), the Netherlands. Health care professionals were surveyed at two time points. In both hospitals, the first survey was conducted towards the end of 2005 prior to implementation of CPOE. The second survey was conducted after CPOE was implemented; for TSh in the summer of 2006 and for UMCC towards the end of 2006 (internal medicine) and in April/May of 2008 (gastroenterology/rheumatology).

Paper-based system versus CPOE

Before the implementation of CPOE on the four medical wards the medication ordering system was paper-based. Physicians wrote prescriptions on forms and nurses transcribed these prescriptions on special administration charts which they used during the process of dispensing and administering.

Following the introduction of CPOE the medication ordering process is computerised. Physicians prescribe the medication in a standardised way. They have to select drugs from menus and are required to fill in various prescription characteristics. Furthermore during the prescribing phase drug safety alerts are generated in case of overdoses and drug-drug interactions. In the two hospitals different CPOE systems are used. The UMCG uses the commercially sold system Medicator® (ISOFT, Leiden, the Netherlands) in contrast to the TSh where the partly homegrown system Theriak® (Theriak evf, Tilburg, the Netherlands) is used. In the Medicator® system only the prescribing phase is computerised (the registration for the dispensing and administration purposes is still paper-based) in contrast to the Theriak® system in which also the patient identification and administration phase is automated.

Implementation of CPOE

The boards of directors of both hospitals enforced their medical wards to implement CPOE. Both hospitals had a systematic approach for the implementation of CPOE. The implementation process was performed by an implementation team consisting of Information and Communication Technology and hospital pharmacy staff. In the UMCG the process took 17 weeks per medical ward. In the TSh it took 10 weeks. Before the implementation the current situation (organisational aspects of the medical ward, procedures and processes) was assessed, technical adjustments were made and physicians and nurses were introduced to and trained in the use

of the system. This introduction was different in both hospitals: demonstrations in the UMCG (passive learning) versus real practicing in prescribing (active learning) in the TSh. During the actual implementation, the implementation team was available to answer questions and solve problems. Finally, the implementation team evaluated the implementation process in a session at each ward with physicians and nurses.

Study population and procedure

The study population consisted of physicians and nurses working on the four study wards. The population was a convenience sample of residents and fellows in internal medicine, specialists, head nurses, coordinating nurses and regular nurses. Per ward at least one supervising specialist and one resident/fellow were approached for the study as well as the head nurse, one coordinating nurse and one regular nurse. The head nurse was asked who of the other nurses had time to participate in the study. Most residents and fellows worked temporarily on a ward and could only be contacted either in the pre- or post-intervention period. The group of respondents in the baseline-period was not the same as in the post-intervention period except for the head nurses. The participants were surveyed in a face-to-face interview by one of three researchers (KV, RZ, JvD).

Questionnaire / interview instrument

Two semi-structured questionnaires were developed targeting physicians and nurses respectively. These surveys were constructed to measure expectations and (composed in a slightly different format) to measure experiences with CPOE.

The overall attitude towards the handwritten and CPOE system was measured by the question "What is your overall opinion about the paper-based system respectively CPOE system?" Respondents could answer 'fine/moderate/neutral/has constraints/completely outdated' for the paper-based system and 'fine (no need for changes)/moderate (there are still some bugs)/neutral/has constraints/does not meet the requirements' for CPOE.

Expectations and experiences with CPOE were measured with statements using a five-point Likert scale, ranging from *1 = completely disagree* through *5 = completely agree*. In an open-ended question respondents were asked to mention advantages as well as disadvantages of the system.

The respondents were asked in structured questions about the preparation, quality and duration of the support from the implementation team. For these questions, also a five-point Likert scale was used.

Data analysis

For the statements the percentage respondents agreeing (score of 4 or 5 on the Likert scale) was calculated. Chi-square tests were used to compare expectations

versus experiences of physicians and nurses and to assess differences between physicians and nurses.

The overall positive view towards CPOE was assessed as a sumscore of eight statements before as well as after the implementation of CPOE: negative statements were recoded into positive statements and the mean number of positive scores over all respondents was calculated. Only the statements were included that were asked both before and after the introduction of CPOE and to both physicians and nurses. A t-test was used for assessing differences in the overall positive view towards CPOE between the two periods. All analyses were performed using SPSS version 14 (SPSS Inc., Chicago, Illinois).

Results

A total of 18 physicians (7 supervising specialists and 11 residents/fellows) and 42 nurses were interviewed **(Table 1)**. The size of the groups before and after the implementation of CPOE was approximately the same for both the physicians and nurses. In the TSh more physicians were surveyed than in the UMCG (12 versus 6), whereas in the UMCG more nurses were included (23 in the UMCG versus 19 in the TSh).

Table 1: characteristics of respondents

			Paper-based system	CPOE
Physicians	n (total = 18)		10	8
	Sex	Female/male	5/5	3/5
	Profession	Resident	1	2
		Fellow	5	3
		Specialist	4	3
	TSh		6	6
	UMCG		4	2
Nurses	n (total = 42)		23	19
	Sex	Female/male	17/6	18/1
	Profession	Head nurse	5	4
		Coordinating nurse	8	7
		Nurse	10	8
	TSh		9	10
	UMCG		14	9

The overall attitude of most physicians and nurses towards the paper-based system was negative **(Figure 1)**. The system was considered to have constraints and

to be completely outdated. In contrast most physicians and nurses experienced CPOE more positively, although they considered it not to be optimal yet because of some technical bugs **(Figure 2)**.

Figure 1: Overall attitude of physicians/nurses towards paper-based system

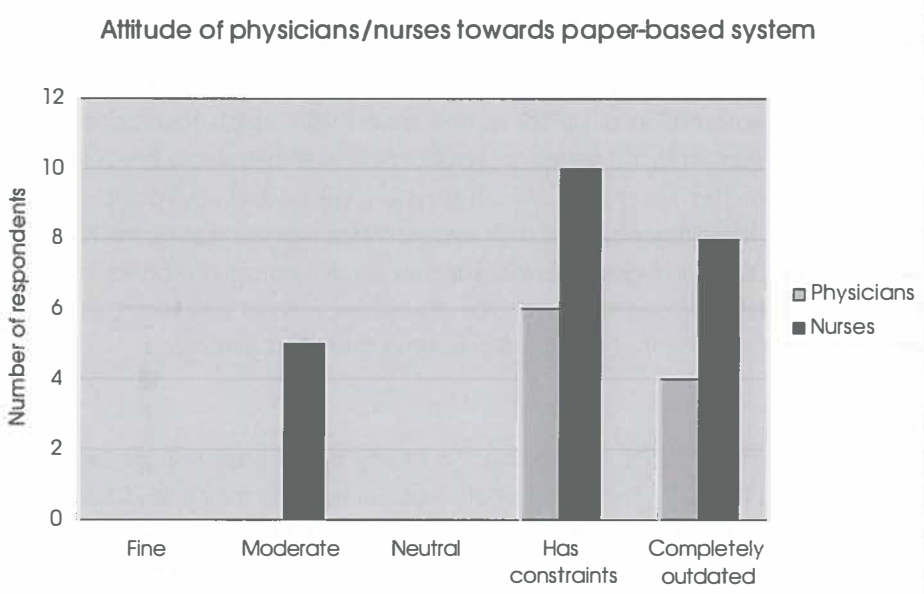
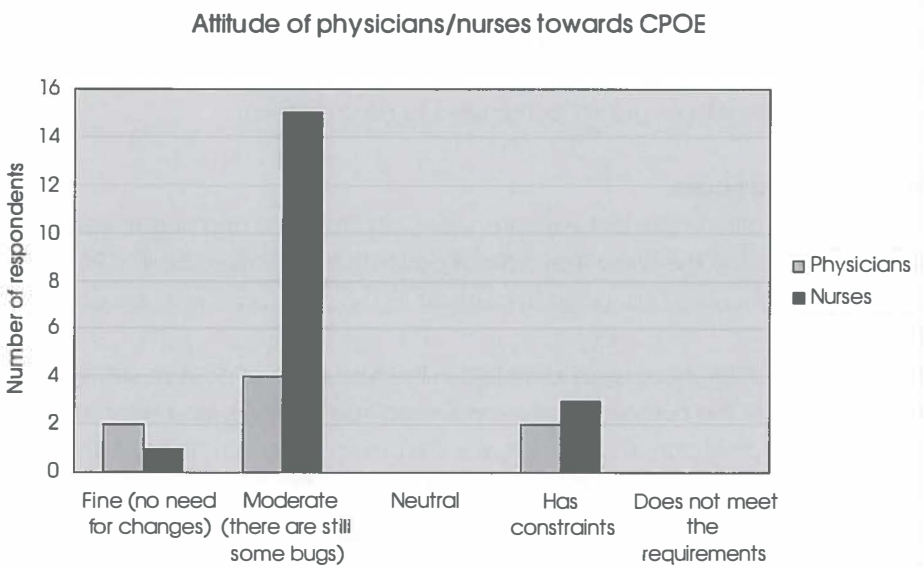


Figure 2: Overall attitude of physicians/nurses towards CPOE



Physicians

Physicians had positive expectations of CPOE being able to reduce prescribing errors and to give an improved overview of patients' medication use which was in line with their experience with CPOE once they had started working with it **(Table 2)**. This was in contrast to the physicians' expectations and experiences with the time it would take to prescribe medication orders by use of CPOE. It turned out to take less time than they had expected. They were neutral before as well as after the implementation of CPOE on the speed with which medication orders were communicated to the nurses and about how well their fellow physicians handled the system. The way nurses used the system exceeded physicians' expectations although the difference with their expectations was not significant. Physicians expected CPOE to give good clinical support on drug-drug interactions but their experiences were less positive (again the difference was not significant). Physicians sticked to their opinion that CPOE still has some technical glitches.

Nurses

Nurses experienced CPOE to improve the clarity of the prescriptions just as they had expected **(Table 2)**. They were positive about the way their fellow nurses cope with the system. Also they were rather positive about CPOE reducing errors in prescribing. Their experiences with the support of CPOE in preventing drug-drug interactions as well as how they experienced that physicians used the system turned out to be significantly worse than their expectations before. A minority of the nurses was positive about the speed with which they were informed about the medication orders. This was found both before (expectations) and after (experiences) the implementation of CPOE. Less technical glitches were experienced than expected, although these glitches are still considered to be a problem.

Physicians and nurses

No significant differences between the views of physicians and nurses were identified except for the overview they had of patients' medication use in CPOE which nurses experienced as not good in contrast to the physicians who experienced it as good.

No significant differences were identified in the sum score of positive views towards CPOE (mean of the number positive answered items) before and after the implementation for physicians (mean before = 4.80, mean after = 5.25, $p = 0.46$) and for nurses (mean before = 4.74, mean after = 4.53, $p = 0.63$). There were also no differences between professions in their overall positive expectations (mean physicians = 4.80, mean nurses = 4.74, $p = 0.91$) nor in their overall positive experiences (mean physicians = 5.25, mean nurses 4.53, $p = 0.20$)

By the introduction of CPOE ...	Physicians		p	Nurses		p
Positive Statements:	Expectations* (n = 10)	Experiences* (n = 8)	value†	Expectations* (n = 23)	Experiences* (n = 19)	value†
Fewer errors in prescribing	100 %	75%	0.09	83%	68%	0.28
A new medication order is sooner known to the nurses	40%	50%	0.67	26%	42%	0.27
A better overview of patients' medication use	90%	88%	0.87	61%	37%	0.12
A good support for preventing of drug-drug interactions	80%	50%	0.18	96%	74%	**0.04**
More clear which medication/dosage the patient should get	-**	-**	-	87%	84%	0.80
The system is user-friendly enough to prescribe in an efficient way	-**	88%	-	-**	-**	-
Negative statements:						
Many (colleague) physicians do not handle the system well, which causes problems	30%	50%	0.39	44%	74%	**0.05**
Many (colleague) nurses do not handle the system well, which causes problems	50%	13%	0.09	48%	32%	0.29
Prescribing takes a lot of time	70%	13%	**0.02**	-**	-**	-
There are still many technical glitches	80%	63%	0.41	87%	47%	**0.01**

* Expressed as percentage agreeing
(positive is defined as scores 4 and 5 on a 5 point Likert scale (1 = strongly disagree and 5 = strongly agree))

† p values refer to chi-square tests for nominal variables

** Not asked

The respondents in both hospitals were satisfied with the implementation process, despite the different approaches used **(Table 3)**. Most of the physicians and nurses reported to be sufficiently prepared to start working with the system. Most professionals present during the implementation process were satisfied with the availability and the available support of the implementation team.
In **box 1** the most frequently mentioned advantages and disadvantages of CPOE are listed. According to the respondents the system improved the efficiency of the medication process and improved the readability of the prescriptions. However, there were still many technical glitches.

Table 3: Experiences with the implementation process

	Physicians (n = 8)	Nurses (n= 19)
You were sufficiently prepared to work with the system?	75%*	90%*
Only for persons who were working at the ward during the implementation:	**(n = 4)**	**(n=18)**
There was enough support from the implementation team during the implementation phase.	100%*	94%*
The implementation team was sufficiently available to give support.	100%*	94%*

* Expressed as percentage agreeing (positive is defined as scores 4 and 5 on a 5 point Likert scale (1 =strongly disagree and 5 = strongly agree))

Box 1: Most listed advantages and disadvantages of CPOE

Advantages	Disadvantages
"System gives a good overview of used medication" (13 times)	"Still many technical glitches" (9 times)
"System is efficient" (13 times)	"Dependence on physicians" (only nurses) (6 times)
"Readability is improved" (11 times)	"System does not give a good overview of used medication" (6 times)
"Fewer medication errors than before" (9 times)	"Too many irrelevant drug-drug interactions" (3 times)
"Introduction of CPOE results in better logistics" (only UMCG) (7 times)	"It is a slow system" (3 times)
"Clinical decision support is incorporated" (6 times)	"Logistics got worse" (only TSh) (2 times)

Discussion

Physicians and nurses were more positive about CPOE than the paper-based medication ordering system. They were also satisfied with the way the system was implemented. In general, their ideas about CPOE before implementation were comparable to their experiences. Even before implementation, a high degree of acceptance of CPOE existed on the work floor which undoubtedly facilitated the actual implementation and adoption. Coupled with the view of professionals that the paper-based system was outdated, this provides good conditions for change.[12] At the same time we have to bear in mind that the use of CPOE was decided at the top of the organisation and once implemented there was no choice at the work floor whether to use CPOE or not.

The most surprising difference between expectations and experiences is with respect to the time investment of prescribing. Prescribing by use of CPOE took less time than the physicians thought it would take. This is in contrast to earlier studies showing that physicians were annoyed with the additional time required for computerised prescribing in comparison to the handwritten way of prescribing.[13, 14] Our more positive findings may be explained by the more user-friendly interfaces that are being used nowadays in comparison with the systems in the nineties described in earlier studies.

In contrast to physicians, nurses were negative about the overview they had of patients' medication use in CPOE. According to them these overviews were not clear. This is certainly a point of interest, because it affects the work process of nurses in a negative way and it can lead to medication errors. Furthermore, the nurses were negative about the way physicians handled CPOE. This may be caused by a change in the way nurses and physicians collaborate since the introduction of CPOE as has been described elsewhere.[8, 15] It is known that in paper-based systems nurses and physicians interact more easily and efficiently with respect to patient's condition and medication.[8] In the CPOE system such interaction is less easy because it separates the work of physicians from that of nurses; the prescribing phase takes place behind a computer with less feedback or information from nurses. Nurses become more dependent on the way physicians prescribe and they have less opportunity to correct physicians' actions.

This study showed that the decision support on drug-drug interactions in CPOE needs more attention. Because in the paper-based system there was limited decision support during the prescribing phase, nurses and physicians' expectations about decision support were high. However these expectations were not met. The

main reason is the generation of too many safety alerts which are not appropriate for the hospital setting. Improvement is needed before 'alert fatigue' occurs, which can lead to ignorance of important alerts besides the unimportant ones.[16] Future research should investigate what the best approach is, as turning off alerts hospital-wide can be problematic because of differences in clinical relevance for the various medical specialties and differences in knowledge.[17]
Despite the difference in strategies for implementing CPOE between both hospitals, physicians and nurses from both hospitals were satisfied with the duration and quantity of the support given by the implementation team. This suggests that both strategies were adequate approaches to implement CPOE, at least well fitted in their context.

The main limitation of this study is the difference in study sample before and after the implementation of CPOE, i.e. few respondents were interviewed twice. Another limitation is the use of a convenience sample instead of a randomised sample. It is possible that our respondents were more willing to participate than other users because they had a clear view towards CPOE, whether positive or negative. A strength of our study is the setting of two hospitals (a university and a teaching hospital) with two different CPOE systems. This enhances the generalisability of our results.

Despite the positive experiences with CPOE, the system does not function optimally yet. Based on the results of this study a number of recommendations can be made on how to optimise the system. First technical glitches should be fixed with a special interest for improving the display of medication overviews for nurses. These glitches are still one of the most frequently mentioned disadvantages of CPOE. Furthermore, the decision support on drug-drug interactions should be improved in the sense that an assessment should be made on which safety alerts are really relevant for the hospital setting and which safety alerts should be turned off for each medical specialty separately. Finally, physicians and nurses should be aware that CPOE has an impact on their collaboration and that during the prescribing process nurses are more dependent on physicians than before. In this situation it is important to guarantee good communication between both professions. Hospitals aiming to start implementing CPOE must take into account these recommendations to guarantee an optimal use of their CPOE system.

Overall we may conclude that physicians and nurses are positive about CPOE and the process of its implementation and do accept these systems. However, these systems should be further improved in order to fit into clinical practice.

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References

(1) *Campbell, E. M., Guappone, K. P., Sittig, D. F., Dykstra, R. H., Ash, J. S. (2009) Computerised provider order entry adoption: implications for clinical workflow. J Gen Intern Med, 24 (1):21-6.*

(2) *Kaushal, R., Bates, D. W. (2002) Information technology and medication safety: what is the benefit? Qual Saf Health Care, 11 (3), 261-5.*

(3) *Kaushal, R., Shojania, K. G., Bates, D. W. (2003) Effects of computerised physician order entry and clinical decision support systems on medication safety: a systematic review. Arch Intern Med , 163 (12), 1409-16.*

(4) *Wolfstadt, J. I., Gurwitz, J. H., Field, T. S., Lee, M., Kalkar, S., Wu, W., Rochon, P. A. (2008) The effect of computerised physician order entry with clinical decision support on the rates of adverse drug events: a systematic review. J Gen Intern Med, 23 (4), 451-8.*

(5) *Ammenwerth, E., Schnell-Inderst, P., Machan, C., Siebert, U. (2008) The Effect of Electronic Prescribing on Medication Errors and Adverse Drug Events: A Systematic Review. J Am Med Inform Assoc , 15 (5), 585-600.*

(6) *Han, Y. Y., Carcillo, J. A., Venkataraman, S. T., Clark, R. S., Watson, R. S., Nguyen, T. C., Bayir, H., Orr, R. A. (2005) Unexpected increased mortality after implementation of a commercially sold computerised physician order entry system. Pediatrics 116 (6), 1506-12.*

(7) *Beuscart-Zephir, M. C., Pelayo, S., Anceaux, F., Meaux, J. J., Degroisse, M., Degoulet, P. (2005) Impact of CPOE on doctor-nurse cooperation for the medication ordering and administration process. Int J Med Inform 2005, 74 (7-8), 629-41.*

(8) *Pirnejad, H., Niazkhani, Z., van der Sijs, H., Berg, M., Bal, R. (2008) Impact of a computerised physician order entry system on nurse-physician collaboration in the medication process. Int J Med Inform 77 (11), 735-44.*

(9) *Koppel, R., Metlay, J. P., Cohen, A., Abaluck, B., Localio, A. R., Kimmel, S. E., Strom, B. L. (2005) Role of computerised physician order entry systems in facilitating medication errors. JAMA 293 (10), 1197-203.*

(10) *Ash, J. S., Sittig, D. F., Seshadri, V., Dykstra, R. H., Carpenter, J. D., Stavri, P. Z. (2005) Adding insight: a qualitative cross-site study of physician order entry. Int J Med Inform , 74 (7-8), 623-8.*

(11) *Aarts, J., Peel, V., Wright, G. (1998) Organizational issues in health informatics: a model approach. Int J Med Inform , 52 (1-3), 235-42.*

(12) *Prochaska, J. O., Velicer, W. F. (1997) The transtheoretical model of health behavior change. Am J Health Promot , 12(1):38-48.*

(13) *Ash, J. S., Gorman, P. N., Hersh, W. R., Lavelle, M., Poulsen, S. B. (1999) Perceptions of house officers who use physician order entry. Proc AMIA Symp 1999;471-5.*

(14) *Weiner, M., Gress, T., Thiemann, D. R., Jenkes, M., Reel, S. L., Mandell, S. F., Bass, E. B. (1999) Contrasting views of physicians and nurses about an inpatient computer-based provider order-entry system. J Am Med Inform Assoc 6 (3), 234-44.*

(15) *Beuscart-Zephir, M. C., Pelayo, S., Anceaux, F., Meaux, J. J., Degroisse, M., Degoulet, P. (2005) Impact of CPOE on doctor-nurse cooperation for the medication ordering and administration process. Int J Med Inform, 74 (7-8), 629-41.*

(16) *van der Sijs, H., Aarts, J., Vulto, A., Berg, M. (2006) Overriding of drug safety alerts in computerised physician order entry. J Am Med Inform Assoc , 13 (2), 138-47.*

(17) *van der Sijs, H., Aarts, J., van Gelder, T., Berg, M., Vulto, A. (2008) Turning off frequently overridden drug alerts: limited opportunities for doing it safely. J Am Med Inform Assoc, 15(4):439-48.*

Chapter 8

Cost-effectiveness of an electronic medication ordering system (CPOE/CDSS) in hospitalised patients

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Abstract

Rationale:
Pharmacotherapy, prescribing medication, is an important aspect of almost all in-hospital treatment regimes. Besides their obviously beneficial effects, medicines can also cause adverse drug events (ADE), which increase morbidity, mortality and health care costs. A part of these ADEs arise from medication errors, e.g. at the ordering stage. ADEs caused by medication errors are preventable ADEs.
Until now, medication ordering was primarily a paper-based process and was thus error prone. Computerised Physician Order Entry, combined with basic Clinical Decision Support System (CPOE/CDSS) is considered to be a useful alternative to enhance patient safety. Limited information is available on the balance between the health gains and the costs that need to be invested in order to achieve these effects.

Objectives:
To study the balance between the effects and costs of CPOE/CDSS compared to the traditional paper-based medication ordering system in a general teaching hospital and a University Medical Centre.

Methodology:
The economic evaluation was performed alongside a clinical study on the effectiveness of CPOE/CDSS. It consisted of a cost minimisation and a cost-effectiveness analysis of CPOE/CDSS compared to the standard paper-based system. All costs of both medication ordering procedures were estimated based on resources used and time invested. Time spent by the health care professionals was calculated based on interviews, questionnaires and actual time registration. Costs of ICT experts were based on the number of full-time equivalents assigned to the CPOE projects in both hospitals. The analyses were performed from a hospital perspective. Since the time horizon did not exceed 1 year, no discounting was applied. Prices were expressed in euros (level 2006).
Outcome measures were medication errors (MEs) and preventable ADEs (pADEs). Results are presented in ratios of incremental costs to incremental effects (ICER). Sensitivity analyses were performed.

Results:
In total 1,195 patients were included; 592 admitted during the paper-based prescribing period, and 603 during the CPOE/CDSS period.

The clinical study showed a decrease in the percentage of medication orders (MOs) containing at least one medication error from 55% with the paper-based system to 17% with CPOE/CDSS, and a decrease in the percentage of patients experiencing at least one pADE from 15.5% to 7.3%.
Total costs of the paper-based system and CPOE/CDSS amounted to € 11.80 and € 14.20 per patient/day respectively. The ICER for errors was 3.38 and for pADEs 307.72, indicating the extra amount (€) that has to be invested in order to prevent one ME or one pADE. Sensitivity analyses on costs and effects showed that the results were quite robust.

Conclusions:
This study showed that CPOE with basic CDSS contributes to a decreased risk of preventable harm. Overall, the extra costs of CPOE/CDSS needed to prevent one ME or one pADE seem to be acceptable, especially in relation to the costs of one ADE or additional admission days.

Introduction

In the Netherlands, every year 1,100 out of 10,000 citizens are admitted to a hospital.[1] Prescription of one or more drugs is an important aspect of almost all hospital treatment regimens. Medication ordering thus can be considered as a regular activity affecting a substantial part of the population. During this process, errors can be made. Studies examining medication errors (MEs), report that 2.9-16.6% of all in-patients experience adverse events serious enough to prolong hospitalisation, cause significant morbidity or even mortality.[2-4] These ADEs caused by medication errors are considered to be preventable ADEs (pADEs). Medication errors in general and the associated awareness of potential harm are a threat to the (subjective) experienced safety of hospitalised patients.

Thus, every possible improvement in the medication ordering process appears to be desirable with regard to health gains, patient wellbeing and experienced safety. However, with regard to a rational spending of the available healthcare budget, it is essential to also study the balance between units of health gained, and the costs that need to be invested in order to achieve these effects.

In most Dutch hospitals, paper-based medication ordering systems are in use, which rely on hand written prescribing and transcribing activities of various health care professionals. Computerised Physician Order Entry (CPOE) systems are considered to be a useful alternative to enhance patient safety. These systems are becoming more common in the Netherlands and a growing body of knowledge on its clinical effectiveness is presented in (inter)national journals. Recently, two systematic reviews were carried out on the effects of CPOE and CPOE with a Clinical Decision Support System (CDSS). The most recent study[5] analysed both MEs and pADEs and concluded that it seems that electronic prescribing can reduce the risk of MEs and pADEs. Wolfstadt et al.[6] looked at the effects of CPOE/CDSS on the rate of pADEs. Results showed that 50% of the included studies reported a significant decrease in pADEs, 40% reported a non-significant reduction in pADEs, and 10% demonstrated no change in pADE rates.

Besides their potential effectiveness, CPOE/CDSS systems are costly.[2,3,7,8] On the other hand, MEs are costly as well. MEs may contribute for an important part to the total number of pADEs. Previous studies estimated that each pADE adds $2,162 to $2,595 (USD) to the costs of hospitalisation and that annual attributable costs for preventable ADEs for a 700 bed teaching hospital are $2.8 million.[2,3,7,8]

At present, limited information is available on the costs and cost-effectiveness of CPOE/CDSS. The few available studies generally show high costs and high cost-effectiveness ratios, which means that the additional costs that have to be invested to gain one unit of additional effect (e.g. reduction in MEs or pADEs) are high.

Kuperman et al[9] reports implementation costs of CPOE for a 500-bed hospital at almost $ 8,000,000 with ongoing annual maintenance costs of $ 350,000. Wu et al[2] performed a cost effectiveness analysis, and found incremental cost-effectiveness ratio of $ 12,700 per ADE averted.

Study design, measures of effect, setting and health care system, however, limit the generalisability of these results. In addition for the European situation we know of no previous cost effectiveness studies on this subject.

Therefore, the aim of the present study was to evaluate the balance between the effects and costs of CPOE compared to a traditional paper-based ordering system.

Methods

Design, population and setting

The economic evaluation was performed alongside an interrupted time series study on the effects of a Computerised Physician Order Entry system , including a basic Clinical Decision Support System (CPOE/CDSS). The effectiveness study was performed in two Dutch hospitals, a University Medical Center (1,300-beds), and a general teaching hospital (500-beds). All patients that were admitted for a duration of at least 24 hours to either the general internal medicine ward, or the gastroenterology ward in the University Medical Center or to the general internal or the geriatric ward of the general teaching hospital were suitable for inclusion. The study was designed as an interrupted time series with two periods of measurement: a pre implementation measurement, in which the paper-based medication ordering system was evaluated, and a post implementation measurement, in which the CPOE/CDS system was evaluated. Data were prospectively collected for 592 patients admitted during twenty weeks before and for 603 patients admitted during twenty weeks after introduction of CPOE/CDSS. Primary outcome measures were the percentage of medication orders with one or more ME and the percentage of patients with one or more pADE.

A waiver of the Medical Ethical Committee was obtained for this study, as the study fell within the boundaries of normal hospital routine of quality improvement. All patients received information about the study and had the opportunity to object to inclusion.

Standard method of prescribing and intervention

The standard (pre intervention) way of prescribing medication was a paper-based system. Physicians wrote prescriptions on forms and nurses transcribed these prescriptions on special administration charts, which they used during the process of dispensing and administering. In the general teaching hospital, MO's were also

entered into the pharmacies computer system for the purpose of medication surveillance.
The intervention, CPOE/CDSS, was a computer-based system by which physicians prescribe medication in an electronically, standardised way. Medicines can be selected from menus in which medication from the local stock or from the pharmacy drug database are shown. In both hospitals different types of CPOE/CDSS systems were used. The University Medical Center used a commercially available system (Medicator®, iSOFT, Leiden, the Netherlands). The general teaching hospital used a partly home-grown system (Theriak® , Theriak evf, Tilburg, the Netherlands), The CDDS system in both Medicator® and Theriak® was basic, meaning that only dosage and drug-drug interaction alerts were generated.

Economic evaluation cost types and cost categories
The economic evaluation consisted of a cost minimisation and a cost-effectiveness analysis of CPOE/CDSS compared to the traditional paper-based medication order system.
Assessing the costs of medication ordering before and after implementing the CPOE/CDSS was an important element of the economic evaluation. Since the economic evaluation was performed from a hospital perspective, all relevant costs related to medication ordering made in the hospital were calculated and taken into account in the cost-effectiveness analysis for all prescriptions of all included patients.

Resource quantities and unit prices
Costs of both medication ordering procedures were assessed. Costs were calculated based on true resources used and time invested, according to the Dutch guidelines for cost-studies.[10] Time spent by various health care professionals was calculated based on interviews (expert opinions), standardised questionnaires, and actual time registration by the researchers. Costs of time spent by ICT experts for maintenance etc. of the computer system and software were calculated based on the number of full-time equivalents assigned to the implementation and maintenance of CPOE/CDSS in both hospitals.

Unit prices for these resources were assessed at the University Medical Center and at the general teaching hospital. The price level used is that of 2006. Prices have been assessed in Euros. **Table** 1 shows the various cost categories and types of costs that have been assessed as well as the method that was used to calculate the costs.

Table 1. Unit prices of included cost categories[1]

Cost category	Method
Medication ordering related activities doctor	Resources used; time investment
Medication ordering related activities nurse	Resources used; time investment
Medication ordering related activities pharmacy staff	Resources used; time investment
Computer system used for medication ordering	Interest and debits 5 years
ICT support and software licence	Resources used; time investment
Implementation process	Resources used; time investment
Housing and overhead	45% of subtotal

[1] *Price level 2006.*

Results are presented in ratios of incremental costs to incremental effects.

$$ICER_{err} = \frac{\text{Additional costs of CPOE/CDSS (compared to paper-based system)}}{\text{MEs averted with CPOE/CDSS (compared to paper-based system)}}$$

$$ICER_{pADE} = \frac{\text{Additional costs of CPOE/CDSS (compared to paper-based system)}}{\text{pADEs averted with CPOE/CDSS (compared to paper-based system)}}$$

The economic evaluation was performed from a hospital perspective. All relevant costs made inside the hospital were taken into account. The time horizon used was the same as that for the clinical study, which means that costs were calculated during the same period the clinical outcomes were measured. That is, from the moment the patient was admitted until discharge.
Since the measurement period did not exceed one year, according to the Dutch guidelines for cost-studies[10] no discounting rate was used in the present study.

Data analysis

Descriptive statistics of the various cost components were performed. In addition univariate and multivariate sensitivity analyses were performed to explore to what extent the cost-effectiveness ratios were influenced by variations in the major cost categories and by variations in de numbers of MEs and pADEs.

Results

Effects

Previous research of our group showed that during the baseline (paper based) period, the mean percentage of MOs containing at least one ME was 55% whereas in the post-intervention period this was 17%. Introduction of CPOE/CDSS led to a significant immediate absolute reduction of 40.3% (95%CI:-45.13;-35.48) of MOs with one or more MEs and a change in trend of -0.92% (95%CI: -1.31; -0.52) per week.

In the baseline period, the mean percentage of admitted patients experiencing at least one pADE was 15.5% in contrast to 7.3% in the post-intervention period. However, since the change is not significant (-0.42, 95% CI:-15.52; 14.68) because of an underlying negative trend at baseline of -4.04% (95% CI: -7.70; -0.38), this decrease could not be attributed to the introduction of CPOE/CDSS.

Costs of the different prescription systems

Cost results for the handwritten, paper-based medication ordering system and the CPOE/CDSS are displayed in table 2. Mean costs of the paper based medication ordering system amounted to € 11.80 per patient per admission day. Mean costs for CPOE/CDSS were € 14.22.The higher costs for CPOE/CDSS were mainly caused by the extra costs for the system (equipment, software and ICT support) and the implementation. Regarding personnel, costs of time investment by the doctor and the pharmacy technician decreased dramatically after the implementation of CPOE/CDSS, whereas the time investment costs of the nurse and to a lesser extent the hospital pharmacist increased.

In separate analyses, differences between hospitals were analysed (results not shown). Differences appeared to be minimal, except for the time investment costs of the pharmacy technician during the paper based medication ordering system. These costs amounted to € 0.16 and € 4.10 per patient per day in the university medical centre and the general teaching hospital respectively. This can be explained by differences in procedures between both hospitals; in the general teaching hospital, central order entry by the hospital pharmacy was in use before electronic medication ordering started, which was time consuming for the pharmacy technicians. Furthermore, pharmacy technicians played a role during patient admission, which was not the case in the university medical centre.

Table 2. Costs of the medication ordering systems per patient/day in Euro (€)

Cost category	Paper-based	CPOE/CDSS
Personnel		
Time investment doctor	3.19	0.81
Time investment nurse	2.37	3.80
Time investment pharmacy technician	2.13	0.77
Time investment hospital pharmacist	0.45	0.93
Equipment (computer, label printer ,server, network.)		0.21
Software		0.23
ICT support and software licence		1.32
Implementation		1.74
Housing and overhead	3.66	4.41
Total	**11.80**	**14.22**

Cost minimisation and cost effectiveness analysis

Based on the overall average of both hospitals, the cost difference (€ 14.22- €11.80) was € 2.42, meaning the computer based prescribing system did cost an extra € 2.42 per patient per day.

Incremental cost-effectiveness ratios (ICER) for both MEs prevented (5724-1355) and pADEs prevented (102-54) are displayed below for the total study population (both hospitals)

$$ICER_{err} = \frac{€\ 14,770.-}{4,369} = 3.38$$

Thus, in order to prevent one extra ME with the electronic medication ordering system, an additional € 3.38 have to be invested compared to the paper based ordering system.

Overall, in order to prevent one extra pADE with the electronic medication ordering system an extra € 307.72 have to be invested compared to the traditional ordering system (see ratio below).

$$ICER_{pADE} = \frac{€\ 14,770.-}{48} = 307.72$$

Sensitivity analyses

In order to study the effects of changes in important cost components on total costs and on cost effectiveness ratios different types of sensitivity analyses were performed. First, cost categories were univariately increased (+20%) or decreased (-20%), or in case of overhead and housing and implementation costs, excluded (-100%).
Effects of varying the different cost categories on the differences in costs between the two methods were minimal. The cost difference between both ordering systems ranged between € 0.10 (paper-based more expensive compared to CPOE/CDSS) and € 2.95 (CPOE more expensive compared to paper-based (original value € 2.42 CPOE/CDSS more expensive compared to paper-based). Excluding the implementation costs (which were only made for CPOE/CDSS) had the biggest influence on the cost difference between the two systems. In this scenario the costs of CPOE/CDSS were lower than those of the paper based system **(table 3)**. As expected, excluding the costs of implementation or overhead and housing had the biggest effect on the ICERs for MEs and pADEs. Excluding the costs of implementation caused the ICERs to become negative. This implies that both MEs/pADEs, and total costs were reduced after the implementation of CPOE/CDSS compared to the paper based system.

Table 3. Univariate sensitivity analysis: effect of varying major cost categories on total costs in Euro (€) and Incremental Cost Effectiveness Ratios (ICER).

Cost category	Variation	Total costs (€) per patient/day			ICER	
		Paper-based system	CPOE/CDSS	Difference	$ICER_{err}$	$ICER_{pADE}$
Original value	*None*	*11.80*	*14.20*	*2.42*	*3.38*	*307.72*
Personnel	+20%	14.16	16.05	1.89	2.14	194.57
	-20%	9.44	12.39	2.95	4.62	419.96
Equipment, software, ICT	+20%	11.80	14.73	2.93	3.49	317.93
	-20%	11.80	13.71	1.91	3.27	297.51
Implementation	+20%	11.80	14.73	2.93	4.34	395.05
	- 20%	11.80	13.72	1.92	2.43	221.23
	- 100%	11.80	11.70	-0.10	-1.57	-142.54
Housing & Overhead	+20%	12.53	15.11	2.58	3.61	328.71
	- 20%	11.07	13.34	2.27	3.00	290.18
	- 100%	8.14	9.81	1.67	1.33	121.23

To create a more extreme scenario compared to the univariate analysis, in a multivariate sensitivity analysis all cost categories in one of both prescribing systems were decreased with 20%, and increased with 20% in the other system. Results of this analysis are displayed in **table 4**. As expected, the difference in costs between the paper based and the CPOE system increased with the multivariate sensitivity analysis. A negative difference (cost savings) was present after increasing the costs of the paper based system with 20%, while at the same time decreasing the costs of CPOE/CDSS with 20%.

Table 4. Multivariate sensitivity analysis: effect of varying major cost categories on total costs in Euro (€) and Incremental Cost Effectiveness Ratios (ICER).

Variation method	Total costs (€) per patient/day			ICER	
	Paper-based system	CPOE/CDSS	Difference	$ICER_{err}$	$ICER_{pADE}$
Original value	*11.80*	*14.20*	*2.42*	*3.38*	*307.72*
All cost categories in paper-based system – 20% and in CPOE system + 20%	8.86	18.13	9.27	16.62	1512.33
All cost categories in paper-based system + 20% and in CPOE system - 20%	15.04	10.67	-4.37	-9.80	-891.87

The effects of the multivariate sensitivity analysis on the ICERs are displayed in **Table 4** and in **figures 1 and 2** (Scenario 1).

Increasing the costs of CPOE/CDSS with 20% while at the same time decreasing the costs of the paper based system, caused a major augmentation of the ICERs, especially the ICER for pADEs. Increasing the costs of the paper based system and decreasing the costs of CPOE/CDSS caused all ICERs to become negative, reflecting both a reduction of MEs/pADEs, and costs with CPOE/CDSS (compared to the paper based system).

In **Figures 1 and 2** results of 4 alternative scenarios of varying the numbers of MEs and pADEs are presented.

In scenario 2 the total numbers of MEs and pADEs were decreased with 20% for both the paper based and CPOE/CDSS and in scenario 3 the total numbers of MEs and pADEs were increased with 20% for both systems. Scenario 4 represents the results of increasing the numbers of MEs and pADEs in the paper based system with 20% and decreasing this number with 20% in CPOE/CDSS and finally, in scenario 5

the numbers of MEs and pADEs in the paper based system were decreased with 20% and in CPOE/CDSS increased with 20%. As expected, scenario 5, in which the number of MEs/pADEs averted with CPOE/CDSS, compared to the paper based system was minimised, had the most dramatic effect. This effect was maximised when hen it was combined with the multivariate sensitivity analyses on costs.

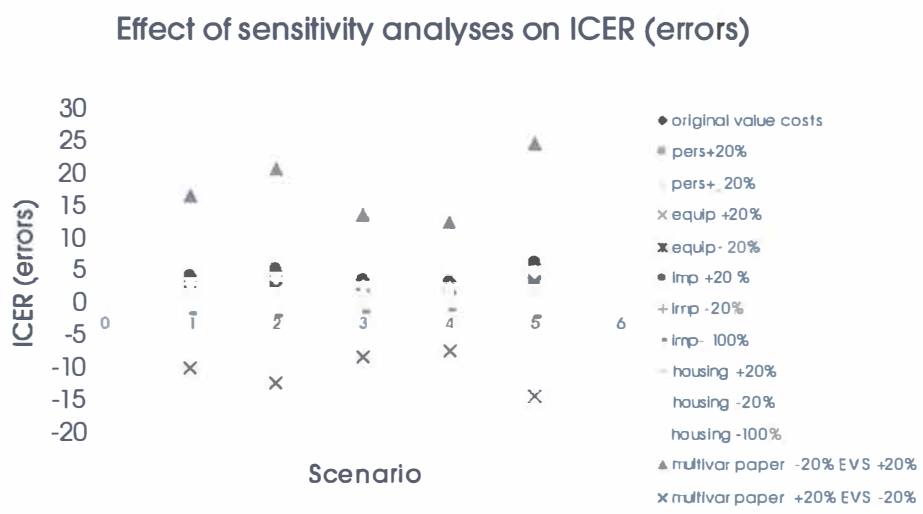

Figure 1. Effect of sensitivity analyses on the ICER (MEs)

Scenario 1: original number of MEs

Scenario 2: 20% decreased in number of MEs for paper-based and CPOE system

Scenario 3: 20% increased in number of MEs for paper-based and CPOE system

Scenario 4: number of MEs 20% increased in for paper-based and 20% decreased for CPOE system

Scenario 5: number of MEs 20% decreased in for paper-based and 20% increased for CPOE system

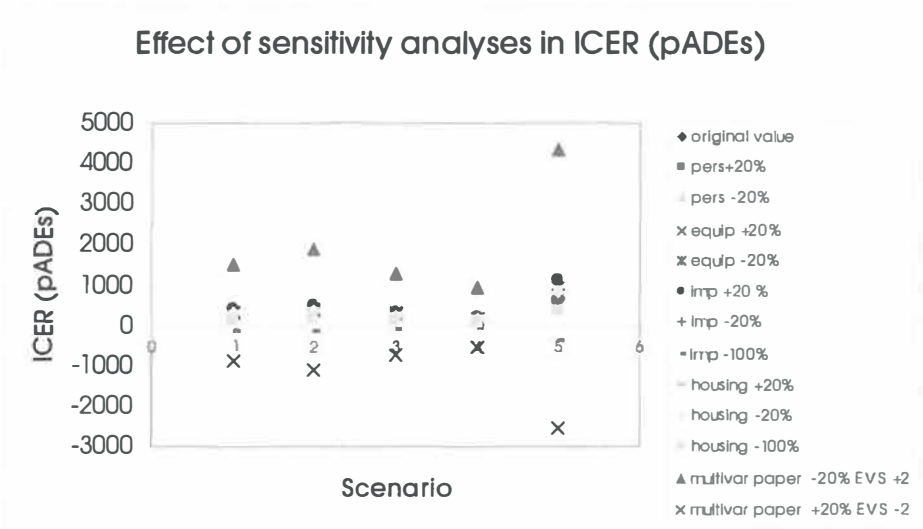

Figure 2. Effect of sensitivity analyses on the ICER (pADEs)

Scenario 1: original number of pADEs

Scenario 2: 20% decreased in number of pADEs for paper-based and CPOE system

Scenario 3: 20% increased in number of pADEs for paper-based and CPOE system

Scenario 4: number of pADEs 20% increased in for paper-based and 20% decreased for CPOE system

Scenario 5: number of pADEs 20% decreased in for paper-based and 20% increased for CPOE system

Discussion

The present study is one of the first that measured and compared both costs and effects on MEs and pADEs of a paper-based medication ordering system and CPOE in different settings. Results showed that overall costs per patient per admission day were € 2.42 higher with the CPOE/CDSS system compared to the paper-based prescribing system. Relative to the total costs of one admission day, which amount to € 495 for a university hospital and € 351 for a general hospital[10] the additional costs appear to be minimal. Still, when considering implementing a new system in medical practice, not only information on costs, but particularly information on the balance between effects (health gains/safety) and costs is essential for the decision. In the present study, the balance between extra costs invested and MEs averted was € 3.38. Extra costs that had to be invested to prevent one extra pADE amounted to € 308,-.To put these figures into perspective, in 2007, Wu et al.[2] found an incremental cost effectiveness ratio of $12,700 per pADE averted. The most important cost components is this study were implementation and training costs, whereas in our study personnel costs of prescribing were the most important.

However, due to the different setting and methodology used in that study, these results are difficult to compare with ours. Data on effectiveness were extracted from a heterogeneous collection of studies looking at ADE rate and effectiveness of CPOE/CDSS. Since developments in computer based systems are quite rapid, present-day systems are difficult to compare to the older ones. The effectiveness studies used in Wu's paper were mostly performed in the nineties. Furthermore, cost effectiveness was estimated over a 10 year horizon.
In our sensitivity analysis it appeared that varying the different cost components had a minor effect on the cost differences between the paper-based and the CPOE system and consequently on the ICERs. Univariate sensitivity analysis on the additional costs of CPOE compared to the paper-based system, showed an upper limit of € 2.95, and a lower limit of
- € 0.10, while the originally calculated value was € 2.42 per patient, per day. This scenario, in which the costs of implementation were excluded, also had a positive effect on the ICER for MEs (-1.57) and pADEs (-142. 54), meaning saving money while at the same time MEs/pADEs were prevented. Overall, different types of sensitivity analyses showed that extra costs that have to be invested with CPOE/CDSS in order to prevent one extra error compared to the paper-based prescribing system, stayed below € 25,-. in all scenarios. For pADEs this value didn't exceed € 2,000,-. except for the most extreme scenario, in which both costs and pADEs where decreased by 20% for paper-based, and increased with 20% for CPOE/CDSS. From literature it is known that the additional costs of one pADE are estimated to vary between $2162 and $2595 (USD).[2,3,7,8] Relative to those costs, the investments needed to prevent one pADE seem reasonable.

An important difference between the paper-based prescribing system and CPOE is the time investment of the nurse. With CPOE in both hospitals the time investment of the nurse increased, while the time investment of the doctor decreased. This was contrary to the increased time investment doctors expected before the implementation of the system. This can probably be explained by the fact that the doctor has to spend less time answering questions concerning illegible handwriting, continuation of certain medication etc. On the other hand, the extra time spend by the nurses mainly has to do with increased time for checking the medication administration charts during the night shift. This takes more time compared to the paper-based system, due to the illogical order of drugs in the medication administration charts (University Medical Centre). From the clinical analysis, it was concluded that there was no significant effect of CPOE/CDSS on the rate of pADEs. This finding may question the relevance of calculating an ICER. However, based on the decline in the absolute proportion of pADEs after implementing CPOE/CDSS, its

clinical relevance and the fact that the cause of the negative trend in pADEs during baseline was unknown, we decided this information was valuable and these ICERs should be presented after all.
Although computer software, maintenance and equipment are an important part of the prescribing system, varying those costs had little effect on total costs and on incremental cost effectiveness ratios. This can be explained by the fact that these costs are a relatively small part of the total costs. Therefore, for policy makers not only the system but also the work processes and the possible changes in these processes should be considered when deciding whether or not to implement an electronic medication ordering system.

In conclusion, the additional costs to prevent one ME are almost negligible, especially compared to the total costs of one admission day. Although in our study we didn't measure patient reported outcome, we feel these extra costs are compensated by the additional effects in terms of ME reduction and possibly increased experienced safety. The latter however, has to be confirmed in additional research.
With regard to the extra costs to prevent one pADE; those are substantially higher compared to the ICER for MEs. However, relative to the additional costs of one pADE, the investments needed to prevent one pADE seem worthwhile.

References

(1) *Statistics Netherlands, http//www.cbs.nl (Last accessed February 2009)*

(2) *Wu, R. C., A. Laporte, and W. J. Ungar. "Cost-effectiveness of an electronic medication ordering and administration system in reducing adverse drug events." J.Eval.Clin.Pract. 13.3 (2007): 440-48.*

(3) *Bates, D. W., et al. "The costs of adverse drug events in hospitalised patients. Adverse Drug Events Prevention Study Group." JAMA 277.4 (1997): 307-11.*

(4) *Pinilla, J., et al. "Case-control analysis of the financial cost of medication errors in hospitalised patients." Eur.J.Health Econ. 7.1 (2006): 66-71.*

(5) *Ammenwerth, E., et al. "The Effect of Electronic Prescribing on Medication Errors and Adverse Drug Events: A Systematic Review." J.Am.Med.Inform.Assoc. 15.5 (2008): 585-600.*

(6) *Wolfstadt, J. I., et al. "The effect of computerised physician order entry with clinical decision support on the rates of adverse drug events: a systematic review." J.Gen.Intern.Med. 23.4 (2008): 451-58.*

(7) *Classen, D. C., et al. "Adverse drug events in hospitalised patients. Excess length of stay, extra costs, and attributable mortality." JAMA 277.4 (1997): 301-06.*

(8) *Senst, B. L., et al. "Practical approach to determining costs and frequency of adverse drug events in a health care network." Am.J.Health Syst.Pharm. 58.12 (2001): 1126-32.*

(9) *Kuperman, G. J. and R. F. Gibson. "Computer physician order entry: benefits, costs, and issues." Ann.Intern.Med, 139.1 (2003): 31-39.*

(10) *Oostenbrink JB. Guidelines for cost studies:methods and unit prices for economic evaluations in health care, rivised version Dutch health Insurance Board. 2004.*

General discussion

A substantial part of the hospitalised patients suffers from harm due to errors occurring in the prescribing process of medication.[1-3] The optimisation of this process will contribute to an increase in medication safety. One approach to this optimisation is the introduction of a Computerised Physician Order Entry system with Clinical Decision Support (CPOE/CDSS) that offers a computerised and standardised way of prescribing with incorporated decision support. Although studies from the USA showed positive effects of these systems in reducing medication errors and adverse drug events, it is important to confirm these effects for the Dutch hospital setting in a study with a robust design. Furthermore, the balance between costs and effects of CPOE/CDSS should be explored because little knowledge exists about the cost-effectiveness of these systems in comparison to the traditional paper-based system. This information is valuable, because presently many hospitals are considering the purchasing of CPOE/CDSS. However, studying the effects of these systems is a challenge because the assessment of medication errors and related patient harm is complex. Various definitions, methodologies and causality assessments exists and the agreement is often not very high between assessors.[4-6] This results in a lack of clarity as to what types of errors are the most relevant from a clinical perspective and what the determinants of errors and adverse drug events are, although these are the main targets for interventions that aim to improve medication safety, such as CPOE/CDSS. Therefore the main objectives of this thesis were:

PART 1: Medication errors and preventable adverse drug events

- to explore methodological aspects of identifying medication errors and adverse drug events and to assess the clinical relevance of medication errors and the determinants of medication errors with and without patient harm

PART 2: CPOE/CDSS in relation to medication safety

- to evaluate what the effect of CPOE/CDSS is on the incidence of medication errors and preventable adverse drug events in two Dutch hospitals
- to explore in depth important features of CPOE/CDSS, namely the effect of clinical decision support (CDSS) on medication safety, the cost-effectiveness of CPOE/CDSS in comparison to the paper-based system and expectations and experiences of health care professionals with CPOE/CDSS.

In this discussion the main findings of the studies will be summarised and presented and the implications for clinical practice and future research will be discussed.

Main findings

In **PART 1** of this thesis we focused on the one hand on the methodological aspects of identifying medication errors and adverse drug events, and on the other hand on the determinants of drug related problems and the clinical relevance of medication errors. We assessed the reliability of the assessment of preventable adverse drug events in daily practice and we explored the impact of the assessors' profession (physician or pharmacist) on reliability (**chapter 2**). We showed that assessing preventable adverse drug events is difficult, because the agreement between individual raters is fair (kappa is 0.36) and the agreement between different professions is moderate (kappa is 0.47). The best approach for assessing preventable adverse drug events is a consensus method, including both physicians and pharmacists as raters. We used a consensus approach in which five pharmacists assessed adverse drug events that were potentially related to errors in the medication ordering process in **chapter 3**. The association between different types of prescribing (administrative, dosing and therapeutic) and transcribing errors and preventable adverse drug events was studied. The results of this study showed that transcribing errors (OR $_{adjusted}$ 1.12; 95% CI 1.01 to 1.25) and therapeutic errors (OR $_{adjusted}$ 1.98; 95% CI 1.53 to 2.56) were significantly associated with pADEs. The association of therapeutic errors was the strongest and from a clinical point of view this type of errors is most relevant. In order to prevent these errors it is important to know their determinants. In **chapter 4** we studied the determinants of medication errors with and without patient harm. A number of determinants were shown to be the same for the two types of medication errors, namely hospital, ward, age of the patient and the therapeutic classes of anti-infectives and neurological medication, although for some of these determinants this was only shown as a non-significant trend. This is probably due to the fact that the number of medication errors leading to patient harm was relatively low, thus resulting in insufficient power of our study. Future studies with larger sample sizes of medication errors leading to harm are needed.

In **PART 2** of this thesis we focused more on CPOE/CDSS in relation to medication safety. We evaluated the effect of CPOE with basic clinical decision support (CDSS) on the incidence of medication errors and preventable adverse drug events in two Dutch hospitals. Results are discussed in **chapter 5**. Introduction of CPOE/CDSS led to a significant immediate absolute reduction of 40.3% (95%CI:-45.13% to 35.48%) of medication orders with one or more errors. In the pre-CPOE/CDSS period, the mean percentage of admitted patients experiencing at least one pADE was 15.5% in contrast to 7.3% in the CPOE/CDSS period. However, this decrease could not be attributed to the introduction of CPOE/CDSS itself. The immediate change was not

significant (-0.42%, 95% CI:-15.52% to 14.68%) because of the observed underlying negative trend during the pre-CPOE/CDSS period of -4.04% (95% CI: -7.70% to -0.38%) per month. More advanced clinical decision support may be needed to reduce the number of preventable adverse drug events. In **chapter 6** we identified to what extent patients at risk for medication related harm as identified by basic CDSS and a set of clinical rules (advanced CDSS) actually need a change in medication. The actual change in medication was determined by medication review. For this study we used a part of the study population as described in chapter 5. Medication review identified 57 overdoses and 143 therapeutic errors in these patients. CDSS identified 297 overdoses, with sensitivity 0.32, specificity 0.92 and positive predictive value (PPV) 0.06; and 365 drug-drug interactions, with sensitivity 0.96, specificity 0.91 and PPV 0.12. The clinical rules identified 78 (39%) of the 200 overdoses and therapeutic errors. In 72 (23 %) of 313 alerts generated a change of medication was actually indicated. When combined CDSS and rules identified 131 (66%) of the 200 errors. The combination of basic CDSS and clinical rules are promising strategies to prevent medication related harm. They will be more useful when they are fine tuned in order to decrease the number of alerts that need no action.

In **chapter** 7 we described expectations and experiences with CPOE/CDSS of physicians and nurses. In general they were positive about the system before as well as after the implementation of CPOE/CDSS. However they think that CPOE/CDS systems can be further optimised, especially regarding technical functioning and incorporated decision support on drug-drug interactions. Finally we studied the balance between the effects and costs of CPOE/CDSS compared to the paper-based medication ordering system in **chapter 8**. Total costs of the paper-based system and CPOE/CDSS amounted to € 11.80 and € 14.20 per patient/day respectively. The ratio of incremental costs to incremental effects (ICER) for medication errors was € 3.38 and for preventable adverse drug events € 307.72, indicating the extra amount of money that has to be invested in order to prevent one medication error or one preventable adverse drug event. Extra costs of CPOE/CDSS needed to prevent one medication error or one preventable adverse drug event seem to be acceptable, especially in relation to the costs of one adverse drug event or additional admission day.

Part 1 - Conclusions and future perspectives on medication errors and preventable adverse drug events

Several studies have been performed in order to assess the incidence of medication errors and (preventable) adverse drug events in different settings.[3, 7-10] There is high variability among the findings of these studies due to the different study

populations and settings but also due to the different methods used to assess medication errors and adverse drug events. The assessment of the relationship between medication errors and patient harm is complex because patient harm can be caused by other factors than medication use, e.g. disease related factors. This assessment will always leave room for subjective interpretation of the rater, leading to lack of agreement between individual raters (this thesis). Therefore the results of medication safety studies based on the assessments of one individual rater may be not reliable. It is necessary to perform this kind of assessments by a panel of raters (at least more than two) and preferably by pharmacists and physicians to combine the more drug oriented view of the pharmacists with the more clinical view of physicians. The fact that only pharmacists were participants in the consensus method of the studies described in the chapters 3 and 5 of this thesis is a limitation. However, in chapter 5 (the effect of CPOE/CDSS on medication safety) we were more interested in the effect of the intervention itself than in the exact incidence of medication errors and preventable adverse drug events. In that situation the most relevant condition is that the same methodology is used before and after the intervention to determine a reliable effect. In our study we assured that the same raters assessed cases in the same systematic way in the pre- as well as in the post-intervention phase.
We may conclude that there still is no method described for the identification of medication error related patient harm that excludes the element of individual judgement, leaving a grey zone around incidence rates. To increase the reliability of these identification methods and to be able to compare incidence rates between different settings (ambulatory care, care institutions, hospitals and different departments in hospitals), standardisation is needed. Both scientists and professionals working in daily practice should reach consensus on what is the best approach for assessing drug related problems. After this has been established, the method should be used in future medication safety studies to draw reliable conclusions about the incidence rates in the different settings.

In this thesis we explored the determinants of medication errors with as well as without patient harm and we studied what subtypes of these errors are mostly associated with patient harm. Due to insufficient power (low number of patients with preventable adverse drug events), only a few determinants of errors with patient harm were found and future research is needed with larger sample sizes of these events. Based on our findings that organisational determinants (e.g. hospital and ward) were significantly associated with both medication errors with and without harm, we may conclude that for these determinants medication errors without harm could be an acceptable interim measure for preventable adverse drug events. For more patient- or medication related determinants these conclusions

can not be drawn and therefore we still have to be careful with using medication errors as interim measures for adverse drug events in studies looking into determinants of drug related problems. When looking at the potential mechanisms associated with medication errors and preventable adverse drug events, the association of medication errors (whether leading to patient harm or not) with organisational characteristics seems plausible and this was indeed confirmed in our study. Furthermore, it seems likely that for medication errors to actually cause patient harm both patient related characteristics (e.g. age, comorbidities) and medication related characteristics (e.g. intrinsic toxicity of the medication) are necessary. Therefore, we can speculate that patient- and medication related determinants would differ for medication errors leading to patient harm, when compared to medication errors not leading to patient harm. However, as said before we could not prove this hypothesis in our study because the sample size was too small.
Despite the low power our study did throw light on the most relevant errors in the medication ordering process in terms of preventing harm to the patient. Therapeutic errors (drug-drug interactions, contra-indications, double medication, improper mono therapy) seemed to be most strongly associated with patient harm. It implies that this type of errors should be the main target for interventions that focus on the reduction of errors in the prescribing process. From both a clinical and scientific point of view these particular interventions might be interesting because they can possibly lead to a significant reduction in preventable adverse drug events. Nevertheless in clinical practice the prevention of other types of prescribing errors can not be left out of consideration because these errors contribute to the potential risk of patient harm. Future research is needed to assess also the clinical relevance of types of errors in other routes of the medication process, such as the administering process or the interface between different settings (hospital and ambulatory care).

Based on the findings in part 1 of this thesis we can conclude the following.
There is need for the standardization of methods for identifying drug related problems, especially the identification of the relationship between medication errors and adverse drug events. The use of one standard method would enable the comparison between incidence rates and determinants of drug related problems in different settings. To assess the current Dutch situation in the future a multi-center study (including different settings as hospital -, ambulatory care and care institutions) should be performed studying the rates and the determinants of drug related problems using the same standard method in all participating centers and should give more understanding in the determinants of adverse drug events because of potential larger sample sizes.
It seems that from a clinical perspective, therapeutic errors are relevant drug related problems. Minimising these errors will lead to the reduction of preventable

patient harm. Therefore strategies aiming at the prevention of therapeutic errors in the prescribing process should be developed and evaluated. Next to the existing computerised clinical decision (see below, part 2) other strategies should for example be the involvement of pharmacists as consultants on hospital wards or in care institutions, the review of patients' medication by physicians and pharmacists together and education of physicians in pharmacotherapy and prescribing of medication. For the evaluation of these interventions, the same systematic method to assess the incidence of preventable patient harm should be used before as well as after the intervention. These kinds of evaluations and studies should not only focus on preventable patient harm but also on patient outcome in general.

Part 2 – Conclusions and future perspectives on CPOE/CDSS in relation to medication safety

In the nearby future, computer technology will be increasingly adopted in efforts to improve the quality and safety of patient care. Computerising the medication process is useful to increase the efficiency in the workflow and may also contribute to improve patient safety, patient outcome and reducing health care costs.[11] In this thesis we focussed on the effects on medication safety and the cost-effectiveness of this technology in comparison to the traditional way of prescribing. In our study into the effect on medication safety we used a more robust design and analysis than the pre/post analyses mainly used in other CPOE/CDSS studies. Our interrupted times series design with segmented linear regression analysis evaluated the longitudinal effect and controlled for trends in the outcomes.[12] We have shown that CPOE/CDSS has a positive effect on medication safety and is cost-effective in comparison to the paper based system. The effect on medication safety is comparable to the findings of other studies: CPOE/CDSS reduces the incidence of medication errors but a decrease in preventable adverse drug events can not always be demonstrated.[13-16] Nevertheless we may conclude that these systems attribute to a decreased risk of preventable harm first because they reduce the number of medication errors of which a significant part could harm patients and secondly because they decrease time spent on correcting errors which could otherwise be spent on primary patient care. However, we have to bear in mind that the implementation of CPOE/CDSS is only the beginning towards high quality prescribing. There is still room for improvement.

Most Dutch CPOE/CDSS systems have a basic form of clinical decision support. In this thesis we have shown that this basic form is not enough to prevent therapeutic errors, the most relevant medication errors in terms of preventing harm to the patient. To achieve a significant effect on preventable adverse drug events, the current clinical decision support must be further developed to fit better into clinical

practice. First of all, there is need for a better balance between warnings of severe and less severe drug related problems. At present all drug-drug interactions and overdoses are shown to all physicians which results in over-alerting and will finally cause alert fatigue.[17] To prevent over-alerting, alerts should be patient-specific and adjusted to the different medical specialties. In the future, consensus should be built among health care professionals on which alerts should be adjusted or turned off. Besides pharmacists also physicians should be participating in this decision-making to increase the acceptability in the field of clinicians. Warnings that are not valued by clinicians will not be effective.

One of the other areas that need to be studied and further developed is what is the best way to present alerts.[18] How to differentiate high-risk situation alerts from low-risk situation alerts? How to present a clear informative description of the drug related problem without leaving room for different interpretations? How to give clear information about what the actions in response to the warning should be? These are all aspects that are important to assess in order to lead to effective decision support.

A next step to increase the impact of clinical decision support on medication safety is to develop and introduce more advanced decision support on top of the already existing decision support such as support on dosing for patients with renal or liver failure, support on therapy for patients with specific risk factors, support on rational drug choice for a certain indication but also reminders when medication monitoring should take place. For most Dutch hospitals the use of this kind of clinical decision support still lies in the future. Some hospital pharmacies are making the first preparations for the implementation of this type of support. Clearly computerised support is a major step forward as a tool in preventing medication related harm in routine practice. The combination of both basic CDSS and clinical rules identified two thirds of the therapeutic medication errors determined in medication review. However, as we have shown in this thesis such efforts should also pay attention to finetuning this support in order to decrease the number of alerts that need no clinical action. For an optimal use and effect of this support, such finetuning should be validated in an expert group of pharmacists and physicians. Only thereafter advanced decision support can be adequately implemented at a large scale in daily clinical practice. Regarding this aspect it is also necessary to pay attention to the possibility to make use of a clinical decision support system in a different way and adapted to the different professionals (e.g. physicians and pharmacists) with their own responsibility.

Technical issues, such as improving the current decision support and developing advanced support, is one aspect needed to be addressed in the implementation of CPOE/CDSS. The other is the organisational embedding of CPOE/CDSS. The introduction of any computer technology should be one of guiding organisational

change by a process of experimentation and mutual learning rather than one of planning, command, and control.[19] Organisations such as hospitals are simultaneously social (e.g. consisting of people, values, norms and culture) and technical (e.g. technology, equipment, procedures). Social and technical elements are deeply interrelated.[20] The implementation of CPOE/CDSS will affect existing processes and workflows and therefore its implementation is not only a change in technology but also in organisation. In this thesis we have shown that physicians and nurses were positive about CPOE/CDSS and the implementation process of this system, but we paid little attention to the organisational aspects. In one of the two hospitals in our study, the implementation process of CPOE/CDSS was seriously delayed because of lack of support of several heads of medical departments. Strategic aspects played an important role in this situation. Another reason was that these physicians believed the system was not yet fitted to their particular situation, i.e. useful when prescribing complex medication protocols for cancer patients. This demonstrates first that it is important that physicians and nurses trust CPOE/CDSS and have a shared vision together with the rest of the organisation towards it. Otherwise this could potentially lead to failure of the implementation. Secondly, it is important to know what the reasons are why physicians consider the system as inappropriate to be able to adapt to physicians' views and feelings. In our example, CPOE/CDSS is still not implemented on the oncology wards. At present, efforts are made to develop a better model of CPOE/CDSS by which complex medication protocols could be prescribed in an efficient and safe way and that is supported by the clinicians.

In this thesis we evaluated the cost-effectiveness of CPOE/CDSS in comparison to the traditional paper based way of prescribing, an important issue for the management and policy makers of healthcare organisations. Only a few other studies performed such a cost-effectiveness analysis and to our knowledge we are the first in the Netherlands. It is clear that more future research is needed into the costs and effects of these systems, especially because presently more and more hospitals are considering implementing CPOE/CDSS. Because there is variation in costs and effects between various hospital settings, data from several other hospitals are needed to come to more robust findings. As we have shown in our sensitivity analyses, differences in costs of CPOE/CDS systems, implementation projects and maintenance processes can lead to different cost-effectiveness ratios. Also differences in incidence rates of medication errors and preventable adverse drug events show variation in results; in settings where medication errors frequently occur (settings with vulnerable and elderly patients) the balance between costs and effects might be more favourable than in settings with lower error rates. Based on our findings we might conclude that for many hospital settings it will be cost-effective

to introduce CPOE/CDSS, certainly if we compare the maximum costs to prevent one medication error and one preventable adverse drug event to the additional costs of one preventable adverse drug event according to other studies.[21-24] Furthermore based on the findings of a recent study in community-based medical practices[25], electronic prescribing might reduce the medication costs when a formulary decision support is incorporated that encourage physicians to prescribe generic or lower-cost alternative medication. This is another way by which CPOE/CDSS offers the opportunity to reduce health care costs. In this situation considering the views of physicians towards using CPOE/CDSS for this purpose is especially important, because physicians may be reluctant to use a system that focuses too clearly on costs in stead of patient care. Furthermore, the case-mix of their patient populations determines to what extent they are capable to prescribe according to the formulary decision support, so the system may prove to be poorly adapted to the physicians' patients.

In our study we have focussed only on the cost-effectiveness of CPOE/CDSS. Future research is needed into the cost-benefit of these systems to take into account the consequences of reduction in medication errors and adverse drug events, namely less treatment, fewer medications administered or shortening of hospital stay. Such a cost-benefit analysis will give a better estimate of the balance between costs and effects than a cost-effectiveness analysis does. However, our study is the first into the aspect of costs of CPOE/CDSS in the Netherlands and will hopefully be a stimulus for more future studies.

Conclusions

In summary, we may conclude that much effort is put into optimising medication safety. CPOE/CDSS is a useful and cost effective tool to support medication safety in hospitals. However, there is still some way to go to improve such systems and other approaches to make the use of medication in hospitals as safe as can be. This provides opportunities for further research into the effects and costs of CPOE, its clinical decision support and advanced support such as the clinical rules. This research should be performed in a reliable way with special interest in the methods of measuring medication safety because identifying medication errors and adverse drug events continues to be a challenge.

References

(1) Kanjanarat P, Winterstein AG, Johns TE, Hatton RC, Gonzalez-Rothi R, Segal R. Nature of preventable adverse drug events in hospitals: a literature review. Am J Health Syst Pharm 2003 September 1;60(17):1750-9.

(2) Gurwitz JH, Field TS, Judge J et al. The incidence of adverse drug events in two large academic long-term care facilities. Am J Med 2005 March;118(3):251-8.

(3) Dean B, Schachter M, Vincent C, Barber N. Prescribing errors in hospital inpatients: their incidence and clinical significance. Qual Saf Health Care 2002 December;11(4):340-4.

(4) Kane-Gill SL, Kirisci L, Pathak DS. Are the Naranjo criteria reliable and valid for determination of adverse drug reactions in the intensive care unit? Ann Pharmacother 2005 November;39(11):1823-7.

(5) Arimone Y, Begaud B, Miremont-Salame G et al. Agreement of expert judgment in causality assessment of adverse drug reactions. Eur J Clin Pharmacol 2005 May;61(3):169-73.

(6) Haynes K, Hennessy S, Morales KH et al. Inter-rater Reliability of a Classification System for Hospital Adverse Drug Event Reports. Clin Pharmacol Ther 2007 August 22.

(7) Krahenbuhl-Melcher A, Schlienger R, Lampert M, Haschke M, Drewe J, Krahenbuhl S. Drug-related problems in hospitals: a review of the recent literature. Drug Saf 2007;30(5):379-407.

(8) Bemt van den PMLA, Egberts ACG. Drug-related problems: definitions and classifications. EJHP 2006;12((suppl.)):10-2.

(9) Lisby M, Nielsen LP, Mainz J. Errors in the medication process: frequency, type, and potential clinical consequences. Int J Qual Health Care 2005 February;17(1):15-22.

(10) Bates DW. Frequency, consequences and prevention of adverse drug events. J Qual Clin Pract 1999 March;19(1):13-7.

(11) Chaudhry B, Wang J, Wu S et al. Systematic review: impact of health information technology on quality, efficiency, and costs of medical care. Ann Intern Med 2006 May 16;144(10):742-52.

(12) Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther 2002 August;27(4):299-309.

(13) Ammenwerth E, Schnell-Inderst P, Machan C, Siebert U. The Effect of Electronic Prescribing on Medication Errors and Adverse Drug Events: A Systematic Review. J Am Med Inform Assoc 2008 September;15(5):585-600.

(14) Wolfstadt JI, Gurwitz JH, Field TS et al. The effect of computerised physician order entry with clinical decision support on the rates of adverse drug events: a systematic review. J Gen Intern Med 2008 April;23(4):451-8.

(15) Eslami S, de Keizer NF, Abu-Hanna A. The impact of computerised physician medication order entry in hospitalised patients--a systematic review. Int J Med Inform 2008 June;77(6):365-76.

(16) Gurwitz JH, Field TS, Rochon P et al. Effect of computerised provider order entry with clinical decision support on adverse drug events in the long-term care setting. J Am Geriatr Soc 2008 December;56(12):2225-33.

(17) van der Sijs H, Aarts J, Vulto A, Berg M. Overriding of drug safety alerts in computerised physician order entry. J Am Med Inform Assoc 2006 March;13(2):138-47.

(18) Kuperman GJ, Bobb A, Payne TH et al. Medication-related clinical decision support in computerised provider order entry systems: a review. J Am Med Inform Assoc 2007 January;14(1):29-40.

(19) Wears RL, Berg M. Computer technology and clinical work: still waiting for Godot. JAMA 2005 March 9;293(10):1261-3.

(20) Berg M, Aarts J, van der Lei J. ICT in health care: sociotechnical approaches. Methods Inf Med 2003;42(4):297-301.

(21) Wu RC, Laporte A, Ungar WJ. Cost-effectiveness of an electronic medication ordering and administration system in reducing adverse drug events. J Eval Clin Pract 2007 June;13(3):440-8.

(22) Bates DW, Spell N, Cullen DJ et al. The costs of adverse drug events in hospitalised patients. Adverse Drug Events Prevention Study Group. JAMA 1997 January 22;277(4):307-11.

(23) Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalised patients. Excess length of stay, extra costs, and attributable mortality. JAMA 1997 January 22;277(4):301-6.

(24) Senst BL, Achusim LE, Genest RP et al. Practical approach to determining costs and frequency of adverse drug events in a health care network. Am J Health Syst Pharm 2001 June 15;58(12):1126-32.

(25) Fischer MA, Vogeli C, Stedman M, Ferris T, Brookhart MA, Weissman JS. Effect of electronic prescribing with formulary decision support on medication use and cost. Arch Intern Med 2008 December 8;168(22):2433-9.

Medicatiefouten en geneesmiddelschade bij opgenomen patiënten: methodologische aspecten en preventie door een elektronisch voorschrijfsysteem.

Een aanzienlijk deel van de in ziekenhuizen opgenomen patiënten ondervindt geneesmiddelschade veroorzaakt door voorschrijffouten. Daarom zal het optimaliseren van het voorschrijfproces bijdragen aan het verbeteren van medicatieveiligheid. Een mogelijkheid tot optimalisatie is het implementeren van een Elektronisch Voorschrijfsysteem met klinische beslissingsondersteuning (EVS). Met dit systeem wordt er geautomatiseerd en gestandaardiseerd voorgeschreven en vindt er medicatiebewaking plaats. Hoewel Amerikaanse onderzoeken een positief effect van dit systeem hebben aangetoond op de reductie van het aantal medicatiefouten en geneesmiddelschade, is het belangrijk dat we dit ook onderzoeken voor de Nederlandse situatie door middel van een onderzoek met een robuust onderzoeksdesign. Daarnaast moet er uitgezocht worden wat de balans tussen kosten en effecten van het EVS is omdat er weinig bekend is over de kosten-effectiviteit van het EVS ten opzichte van het handgeschreven systeem. Dit is belangrijke informatie aangezien veel ziekenhuizen in Nederland bezig zijn met de aanschaf van een EVS.

Het is een uitdaging om de effecten van dit systeem in kaart te brengen omdat de beoordeling van medicatie fouten en geneesmiddelschade zeer complex is mede door de verschillende definities, methodes en causiliteitsbepalingen die gebruikt worden. Bovendien is vaak ook de overeenstemming in uitkomsten tussen de verschillende beoordelaars niet erg hoog. Dit leidt tot onduidelijkheid welk type fouten het meest klinisch relevant zijn en wat de determinanten voor het ontstaan voor medicatiefouten en geneesmiddelschade zijn. Toch zijn dit meestal de aspecten waar interventies die verbetering van medicatieveiligheid beogen (zoals onder andere het EVS) zich op richten. Daarom zijn de belangrijkste onderzoeksvragen van dit proefschrift:

Deel 1: Medicatiefouten en voorkombare geneesmiddelschade

- Het onderzoeken van methodologische aspecten rondom het identificeren van medicatiefouten en geneesmiddelschade. Het beoordelen van de klinische relevantie van medicatiefouten en het beoordelen van de determinanten van medicatiefouten zowel met als zonder geneesmiddelschade.

Deel 2: Het EVS in relatie tot medicatieveiligheid

- Het evalueren van het effect van het EVS op de incidentie van medicatiefouten en voorkombare geneesmiddelschade in twee Nederlandse ziekenhuizen
- Het nader evalueren van bepaalde kenmerken van het EVS, namelijk het effect van medicatiebewaking /beslissingsondersteuning op medicatieveiligheid en de kosten-effectiviteit van het EVS in vergelijking met het handgeschreven systeem. Het in kaart brengen van de verwachtingen en ervaringen met het EVS van professionals in de gezondheidszorg.

In dit deel zullen de belangrijkste resultaten van het proefschrift worden beschreven en komen de implicaties voor de klinische praktijk en eventuele aanbevelingen voor volgende onderzoeken aan bod.

Resultaten

In het eerste deel van het proefschrift richtten we ons ten eerste op de methodologische aspecten rondom het identificeren van medicatiefouten en geneesmiddelschade en ten tweede op de determinanten van geneesmiddel gerelateerde problemen en de klinische relevantie van medicatiefouten. We beoordeelden de betrouwbaarheid van de beoordeling van voorkombare geneesmiddelschade in de dagelijkse klinische praktijk. Daarnaast bepaalden we de invloed van de professionele achtergrond van de beoordelaars (arts of apotheker) op de betrouwbaarheid **(hoofdstuk 2)**. We hebben aangetoond dat het beoordelen van voorkombare geneesmiddelschade moeilijk is, omdat de overeenstemming tussen individuele beoordelaars matig (kappa is 0.36) en de overeenstemming tussen de verschillende professies redelijk is (kappa is 0.47). De beste oplossing voor het beoordelen van voorkombare geneesmiddelschade is een consensus methode waarbij zowel artsen als apothekers beoordelaars zijn. Hoewel deze gemengde samenstelling van het beoordelingspanel het meest optimaal zou zijn, gebruikten we in **hoofdstuk 3** een consensus methode waarbij vijf apothekers beoordeelden of patiëntschade potentieel veroorzaakt was door fouten in het voorschrijf proces. We onderzochten de associatie tussen aan de éne kant de verschillende typen voorschrijffouten (administratieve fouten, doseerfouten en therapeutische fouten)

en overschrijffouten en aan de andere kant voorkombare geneesmiddelschade. Uit de resultaten van dit onderzoek bleek dat de associaties tussen zowel overschrijffouten ($OR_{gecorrigeerd}$ 1,12; 95% betrouwbaarheidsinterval:1,01 tot 1,25) en voorkombare geneesmiddelschade als therapeutische fouten ($OR_{gecorrigeerd}$ 1,98; 95% BI:1,53 tot 2,56) en voorkombare geneesmiddelschade significant waren. De laatste associatie (therapeutische fouten) was het sterkste en vanuit klinisch oogpunt is dit type medicatiefout het meest relevant. Om te onderzoeken of de determinanten van fouten met voorkombare geneesmiddelschade dezelfde zijn als die van fouten zonder voorkombare geneesmiddelschade bestudeerden we in **hoofdstuk 4** de determinanten van beide soorten medicatiefouten. Een aantal determinanten bleken hetzelfde te zijn voor medicatiefouten met en zonder geneesmiddelschade: het ziekenhuis, de afdeling, leeftijd van de patiënt, de geneesmiddelgroep antibiotica en middelen bij neurologische aandoeningen. Echter, voor sommige van deze determinanten resulteerde dit alleen in een niet significante trend. Dit werd waarschijnlijk veroorzaakt door het lage aantal medicatiefouten met geneesmiddelschade en dus een te lage power van ons onderzoek. Daarom is het belangrijk dat toekomstige onderzoeken grotere studiepopulaties (= medicatiefouten met geneesmiddelschade) gebruiken.

In het tweede deel van dit proefschrift richtten we ons meer op het EVS in relatie tot medicatieveiligheid. We evalueerden het effect van het EVS op de incidentie van medicatiefouten en voorkombare geneesmiddelschade in twee Nederlandse ziekenhuizen. De resultaten zijn besproken in **hoofdstuk 5**. De implementatie van het EVS veroorzaakte een significante onmiddellijke reductie van 40,3% medicatieopdrachten met één of meer fouten (95% BI:-45,13% tot -35,48%). In de baseline periode was het gemiddelde percentage van opgenomen patiënten dat voorkombare geneesmiddelschade ondervond 15,5% in tegenstelling tot 7,3% in de post interventie periode. Deze afname kon echter niet worden toegeschreven aan de daadwerkelijke implementatie van het EVS: de onmiddellijke afname was niet significant (-0,42%; 95% BI:-15,52% tot14,68%) vanwege een onderliggende negatieve trend gedurende de baseline periode van -4,04% per maand (95% BI: -7,70% tot -0,38%). Waarschijnlijk is er behoefte aan een meer geavanceerde medicatiebewakingsmodule in het EVS en meer beslissingsondersteuning om voorkombare geneesmiddelschade te reduceren. In **hoofdstuk 6** onderzochten we hoeveel van de patiënten die volgens de medicatiebewakingsmodule van het EVS en een kleine set van klinische beslisregels risico liepen op geneesmiddelschade ook daadwerkelijk een aanpassing in hun medicatie nodig hadden. Dit laatste werd bepaald aan de hand van een medicatie review methode. In dit onderzoek maakten we gebruik van een deel van de onderzoekspopulatie beschreven in **hoofdstuk 5**. Met behulp van de medicatie review methode werden

57 overdoseringen en 143 therapeutische fouten geïdentificeerd in de medicatie van deze patiënten. De medicatiebewakingsmodule identificeerde 297 overdoseringen (met een sensitiviteit van 0,32, een specificiteit van 0,92 en een positief voorspellende waarde van 0,06) en 365 geneesmiddelinteracties (met een sensitiviteit van 0,96, een specificiteit van 0,91 en een positief voorspellende waarde van 0,12). De set klinische beslisregels identificeerde 78 (39%) van de in totaal 200 overdoseringen en therapeutische fouten. In 72 (23%) gevallen van de 313 gegenereerde signalen was er ook daadwerkelijk een aanpassing in de medicatie nodig. De combinatie van de medicatiebewakingsmodule en de set klinische beslisregels identificeerde 131 (66%) van de 200 medicatiefouten. Deze combinatie van verschillende vormen van voorschrijfondersteuning biedt toekomstperspectief in het voorkomen van geneesmiddelschade, zeker wanneer er aandacht besteed wordt aan het reduceren van overbodige signalen.
In **hoofdstuk** 7 beschreven we de verwachtingen en ervaringen met het EVS van artsen en verpleegkundigen. Beide groepen waren in het algemeen positief over het systeem, zowel voor als na de implementatie. Wel gaven ze aan dat het systeem verder geoptimaliseerd moet worden met name op het gebied van de medicatiebewaking van geneesmiddelinteracties en het technisch functioneren van het systeem.
Als laatste onderzochten we in **hoofdstuk 8** de balans tussen de effecten en kosten van het EVS in vergelijking met het handgeschreven systeem. De totale kosten van het handgeschreven systeem en het EVS waren € 11,80 respectievelijk € 14,20 per patiënt per dag. De ratio van incrementele kosten tot incrementele effecten was € 3,38 voor medicatiefouten en € 307,72 voor voorkombare geneesmiddelschade. Deze ratio geeft de extra hoeveelheid geld weer die moet worden geïnvesteerd om één medicatiefout of één voorkombare bijwerking te voorkomen. De extra kosten lijken acceptabel, zeker in vergelijking met de kosten die gepaard gaan met geneesmiddelschade of een ziekenhuisopnamedag.

Deel 1 - Conclusies en toekomstperspectief op het gebied van medicatiefouten en voorkombare geneesmiddelschade

Verscheidene onderzoeken zijn uitgevoerd om de incidentie van medicatiefouten en (voorkombare) geneesmiddelschade te bepalen in verschillende settings. Door de verschillende onderzoekspopulaties, settings en gebruikte methoden is de variatie in de resultaten groot. Daarnaast is de beoordeling van de relatie tussen medicatiefouten en patiëntschade complex omdat patiëntschade ook door andere factoren dan geneesmiddelgebruik veroorzaakt kunnen worden, bijvoorbeeld ziekte gerelateerde factoren. Daarom laat deze beoordeling altijd ruimte open voor een subjectieve interpretatie van de beoordelaar, wat soms leidt tot een

lage overeenstemming tussen individuele beoordelaars (dit proefschrift). Daarom zijn resultaten van medicatieveiligheidsonderzoeken gebaseerd op de beoordeling van één beoordelaar mogelijk niet betrouwbaar. Het is belangrijk om deze beoordelingen door een panel van meerdere beoordelaars (meer dan twee) uit te voeren. Bovendien gaat de voorkeur ernaar uit om zowel artsen als apothekers in het panel te betrekken om zowel de klinische blik van de artsen met de meer geneesmiddel georiënteerde blik van de apothekers te combineren. Het feit dat alleen apothekers betrokken waren bij de consensus methode in de onderzoeken beschreven in de hoofdstukken 3 en 5 is een beperking van dit proefschrift. Echter, in hoofdstuk 5 (het effect van het EVS op medicatieveiligheid) waren we meer geïnteresseerd in het effect van de interventie zelf (EVS) dan de daadwerkelijke incidentie van medicatiefouten en voorkombare geneesmiddelschade. In een dergelijke situatie is het belangrijk dat dezelfde methode zowel voor als na de interventie gebruikt wordt. In ons onderzoek hebben we zorg gedragen dat de data op dezelfde systematische wijze werden beoordeeld in zowel de baseline periode als de post interventie periode.
We kunnen concluderen dat er nog steeds geen methode voor het identificeren van medicatiefouten gerelateerde geneesmiddel schade bestaat die de individuele (subjectieve) beoordeling uitsluit. Het ontbreken van deze methode leidt nog altijd tot een grijs gebied rondom incidentie cijfers. Om aan de éne kant de betrouwbaarheid van de bestaande methodes te verbeteren en aan de andere kant de incidentie cijfers in verschillende settings (eerste lijn, verpleeghuizen, ziekenhuizen en verschillende afdelingen van ziekenhuizen) met elkaar te kunnen vergelijken, is standaardisatie van methodes nodig. Zowel wetenschappers als professionals in de gezondheidszorg moeten consensus bereiken over wat de beste benadering is om geneesmiddel gerelateerde problemen te beoordelen. Hierna kan deze methode gebruikt worden in toekomstige medicatieveiligheidsonderzoeken zodat er betrouwbaardere conclusies kunnen worden getrokken over de incidentie cijfers van geneesmiddel gerelateerde problemen in de verschillende settings.

In dit proefschrift onderzochten we de determinanten van medicatiefouten met en zonder geneesmiddelschade en we bestudeerden welke subtypen medicatiefouten het meest geassocieerd waren met geneesmiddelschade. Vanwege onvoldoende power van ons onderzoek (een te laag aantal patiënten met voorkombare geneesmiddelschade) konden we weinig determinanten voor medicatiefouten met geneesmiddelschade aantonen. In de toekomst moeten er onderzoeken worden uitgevoerd met grotere studiepopulaties. Uit onze resultaten bleek dat determinanten op het vlak van organisatie (bijvoorbeeld het ziekenhuis en de afdeling) significant geassocieerd waren met medicatiefouten met en zonder

geneesmiddelschade. We kunnen concluderen dat betreft deze determinanten medicatiefouten zonder geneesmiddelschade als interim uitkomstmaat kunnen fungeren voor voorkombare geneesmiddelschade. Echter, voor de determinanten op het vlak van de patiënt en medicatie kunnen deze conclusies niet worden getrokken en daarom moeten we nog steeds terughoudend zijn met het gebruik van medicatiefouten zonder geneesmiddelschade als interim uitkomstmaat. Wanneer we de potentiële achterliggende mechanismen van het ontstaan van medicatiefouten en voorkombare geneesmiddelschade in ogenschouw nemen, dan lijkt de associatie tussen medicatiefouten (zowel met als zonder schade) en organisatiekenmerken logisch. Verder lijkt het waarschijnlijk dat bepaalde patiëntkenmerken (zoals leeftijd en co-morbiditeit) en bepaalde geneesmiddelkenmerken (zoals de intrinsieke toxiciteit van het geneesmiddel) een voorwaarde zijn voor het totstandkomen van geneesmiddelschade. Dit zou een mogelijke oorzaak kunnen zijn voor het feit dat patiënt en geneesmiddel gerelateerde determinanten voor medicatiefouten zonder schade niet dezelfde zijn als voor medicatiefouten met schade. We hebben deze hypothese echter niet kunnen bevestigen vanwege een te kleine onderzoekspopulatie.
Desondanks hebben we kunnen aantonen welk type medicatiefout in het voorschrijfproces het meest relevant is in het kader van voorkomen van patiëntschade. Dit bleken therapeutische fouten (geneesmiddelinteracties, gecontraïndiceerde medicatie, dubbelmedicatie, onterechte mono therapie) te zijn. Dit betekent dat dit type fout de belangrijkste focus voor interventies gericht op het verminderen van fouten in het voorschrijfproces moet zijn. Vanuit klinisch en wetenschappelijk oogpunt zijn deze interventies belangrijk omdat ze mogelijk voorkombare geneesmiddelschade significant kunnen verminderen. Niettemin moet er ook aandacht besteed worden aan interventies gericht op andere typen voorschrijffouten omdat deze in potentie ook geneesmiddelschade kunnen veroorzaken. Toekomstig onderzoek moet zich richten op de klinische relevantie van fouten in andere fasen van het medicatie proces, zoals het toedienen van geneesmiddelen en de overdracht van medicatiegegevens tussen de eerste en tweede lijn.

We kunnen het volgende concluderen op basis van de resultaten uit het eerste gedeelte van dit proefschrift:
Er is behoefte aan de standaardisatie van methoden voor het identificeren van geneesmiddel gerelateerde problemen. Dit betreft zeker de methoden voor het bepalen van de relatie tussen medicatiefouten en geneesmiddelschade. Door het gebruik van één standaardmethode zijn incidentie cijfers en determinanten voor geneesmiddel gerelateerde problemen beter te vergelijken tussen verschillende settings. Daarom is er vraag naar een multi center onderzoek met een grote populatie waarbij deze aspecten door middel van een standaardmethode in

de verschillende settings (in de eerste lijn, tweede lijn en verpleeghuizen) in kaart wordt gebracht voor de Nederlandse situatie.
Vanuit klinische oogpunt blijken therapeutische fouten relevant te zijn. Het minimaliseren van deze fouten zal leiden tot het verminderen van voorkombare geneesmiddelschade. Interventies gericht op dit type fout moeten verder ontwikkeld en geëvalueerd worden. Hierbij moet gedacht worden aan geautomatiseerde medicatiebewaking (zie verder, deel 2), maar ook aan de rol van (ziekenhuis)apothekers als consulenten op verpleegafdelingen, het gezamenlijk beoordelen van medicatieoverzichten door artsen en apothekers en verbetering van het onderwijs aan artsen in het voorschrijven van medicatie. Onderzoeken die deze interventies evalueren moeten ervoor zorgen dat zowel voor als na de interventie dezelfde systematische methode om geneesmiddel gerelateerde problemen in kaart te brengen, wordt gebruikt. Deze onderzoeken moeten naast voorkombare geneesmiddelschade ook meer algemeen patiënt gerelateerde uitkomstmaten meenemen, zoals lengte van ziekenhuisopname, heropnames, morbiditeit en mortaliteit.

Deel 2- Conclusies en toekomstperspectief op het gebied van het EVS in relatie tot medicatieveiligheid

Computer technologie zal in de toekomst steeds meer zijn intrede nemen in de gezondheidszorg om de kwaliteit en veiligheid van deze zorg te verbeteren. De automatisering van het medicatie proces zal leiden tot een efficiënter verloop van werkprocessen, verbetering van patiëntveiligheid en een afname van de gezondheidskosten. In dit proefschrift hebben we gekeken naar het effect van deze computer technologie op medicatieveiligheid en de kosten-effectiviteit van deze technologie ten opzichte van het handgeschreven systeem. In ons onderzoek naar het effect op medicatieveiligheid gebruikten we een meer robuust onderzoeksdesign en een robuustere analyse in vergelijking met de designs en pre - post analyses die de meeste andere EVS onderzoeken hebben toegepast. Het 'interrupted time series' onderzoeksdesign met de gesegmenteerde regressie analyse stelden ons in staat om het lange termijn effect van het EVS te evalueren en om te corrigeren voor eventuele trends in de uitkomstmaten. We hebben aangetoond dat het EVS een positief effect heeft op medicatieveiligheid en dat het systeem kosten-effectief is ten opzichte van het handgeschreven systeem. Het effect op medicatieveiligheid is vergelijkbaar met de resultaten van andere onderzoeken: de implementatie van een EVS leidt weliswaar tot de reductie van medicatiefouten maar een effect op voorkombare geneesmiddelschade is niet altijd aantoonbaar.Toch kunnen we concluderen dat deze systemen bijdragen aan een afname van het risico op voorkombare geneesmiddelschade, enerzijds omdat ze het aantal medicatiefouten verminderen waarvan een deel potentieel tot schade kan leiden, anderzijds omdat ze

meer tijd creëren voor patiëntenzorg omdat er minder medicatiefouten hoeven te worden gecorrigeerd. Wel moeten we ons beseffen dat de implementatie van het EVS pas één van de eerste stappen is richting hoogwaardig voorschrijven, aangezien er nog steeds ruimte blijft voor verbetering.
De meeste Nederlandse elektronisch voorschrijfsystemen hebben een basis vorm van medicatiebewaking (alleen controle op overdoseringen, geneesmiddelinteracties en dubbelmedicatie). We hebben in dit proefschrift aangetoond dat deze basis vorm niet voldoende is om therapeutische fouten, vanuit klinische oogpunt de meest relevante voorschrijffouten, te voorkomen. Om een effect te bereiken zal de huidige vorm van medicatiebewaking verder ontwikkeld moeten worden om beter te kunnen functioneren in de klinische praktijk.
Ten eerste is er behoefte aan een betere balans tussen signalen die een ernstig en minder ernstig geneesmiddel gerelateerd probleem aan de orde stellen. Momenteel zijn alle geneesmiddelinteracties en overdoseringen zichtbaar voor alle artsen, wat leidt tot een overmaat aan signalen. Uiteindelijk draagt dit bij aan 'signaal vermoeidheid'. Om deze vermoeidheid tegen te gaan is het belangrijk dat de signalen meer toegespitst worden op individuele patiënten en dat ze aangepast worden aan de verschillende medische specialismen. Het is dan ook belangrijk dat er consensus wordt bereikt onder de verschillende professionals welke signalen aangepast moeten worden en welke eventueel uitgezet kunnen worden. Naast apothekers moeten ook artsen betrokken zijn bij deze beslissingen. Signalen waar voorschrijvers geen waarde aan hechten zullen niet effectief zijn en zullen leiden tot weinig draagvlak in de kliniek.
Ten tweede moet er meer aandacht besteed worden aan de manier waarop de verschillende signalen aan de voorschrijver worden gepresenteerd. Hoe kunnen we goed onderscheid maken tussen signalen met een hoog risico op schade en signalen met een laag risico? Hoe kunnen we goede, duidelijke informatie geven over het risico zonder het gevaar op verschillende manieren van interpretatie? Hoe moeten we duidelijk aangeven wat de actie op het signaal moet zijn? Dit zijn allemaal zaken die aan de orde moeten komen om een effectieve vorm van medicatiebewaking/beslissingsondersteuning te bewerkstelligen.

Een volgende stap om het effect van de medicatiebewakingsmodule/beslissingsondersteuning te vergroten is het ontwikkelen en introduceren van meer geavanceerde beslissingsondersteuning bovenop de al bestaande vorm. We moeten hierbij bijvoorbeeld denken aan doseringsondersteuning bij patiënten met nier- en leverfunctiestoornissen, ondersteuning bij therapie voor patiënten met bepaalde risicofactoren, ondersteuning bij geneesmiddelkeuze bij bepaalde indicaties en ook signalen wanneer geneesmiddelspiegels bepaald moeten worden. Het gebruik van deze meer geavanceerde ondersteuning is voor de meeste Neder-

landse ziekenhuizen nog steeds toekomstmuziek. Sommige ziekenhuisapotheken zijn echter al bezig met de eerste stappen richting gebruik van deze ondersteuning.

Het is duidelijk dat geautomatiseerde ondersteuning zal bijdragen aan het voorkomen van geneesmiddelschade in de klinische praktijk. In dit proefschrift hebben we aangetoond dat de basis vorm van medicatiebewaking samen met een kleine set van klinische beslisregels 2/3 van het aantal therapeutische fouten en overdoseringen (geïdentificeerd mbv medicatie review) signaleerde. Toch moet er aandacht besteed worden aan het verfijnen van deze vorm van beslissingsondersteuning, zeker op het vlak van de hoeveelheid signalen waarbij geen actie nodig is. Het verder ontwikkelen en aanpassen moet plaats vinden in een expert groep van artsen en apothekers. Alleen onder die voorwaarde kan worden begonnen met het grootschalig toepassen van dit soort systemen in de hele kliniek.

Tot nu toe hebben we het alleen nog maar gehad over de technische aspecten van het EVS zoals het optimaliseren van de medicatiebewaking/beslissingsondersteuning. Een ander belangrijk aspect is de inbedding van dergelijke systemen in de organisatie. De implementatie van computer technologie bestaat uit de begeleiding van een organisatieverandering. Bij voorkeur zou deze begeleiding gepaard moeten gaan met een proces van experimenteren en wederzijds leren en niet met een proces van plannen, uitvoeren en controleren. Organisaties zoals ziekenhuizen hebben aan de éne kant sociale elementen (bestaan uit personen, hebben eigen waarden en normen en een eigen cultuur) en aan de andere kant technische elementen (hebben technologie, apparatuur en procedures). Beide soorten elementen zijn nauw met elkaar verbonden. De implementatie van een EVS zal van invloed zijn op bestaande procedures en werkprocessen en zal daarom niet alleen een verandering teweeg brengen in de technologie maar ook in de hele organisatie. Alhoewel we in dit proefschrift hebben aangetoond dat artsen en verpleegkundigen positief waren over het EVS en de implementatie van het EVS, hebben we weinig aandacht besteed aan de organisatieverandering. In één van de ziekenhuizen, betrokken bij ons onderzoek, liep de implementatie van het EVS vertraging op vanwege te weinig draagvlak bij de hoofden van een aantal medische verpleegafdelingen. Eén van de redenen dat er weinig draagvlak was onder de afdelingshoofden was dat ze het EVS niet geschikt achtten voor het voorschrijven van ingewikkelde cytostatica kuren aan oncologie patiënten. Dit laat ten eerste zien dat het belangrijk is dat de gebruikers van het EVS vertrouwen hebben in het systeem en dezelfde ideeën hebben over het systeem als de rest van de organisatie. Is dit niet het geval, dan leidt dit mogelijk tot het falen van het implementatie proces. Ten tweede is het belangrijk om aandacht te besteden aan de redenen waarom EVS-gebruikers bezwaren zien tegen het gebruik van het systeem. In het betreffende ziekenhuis uit ons onderzoek wordt er nog steeds niet elektronisch voor-

geschreven op de oncologie afdelingen. Momenteel is men bezig om een speciale module voor het EVS te ontwikkelen waarmee complexe cytostatica kuren op een efficiënte en veilige manier kunnen worden voorgeschreven en die gedragen wordt door de voorschrijvers.

We hebben in dit proefschrift de kosten-effectiviteit van het EVS geëvalueerd ten opzichte van het handgeschreven systeem. Deze evaluatie biedt belangrijke informatie voor zowel het management als beleidsmedewerkers van gezondheidszorg organisaties. Er zijn maar weinig onderzoeken die een dergelijke kosten-effectiveitsanalyse hebben uitgevoerd en voor zover wij weten is ons onderzoek de enige in Nederland. In de toekomst is er zeker plaats voor meer onderzoeken naar de kosten en effecten van deze systemen aangezien steeds meer ziekenhuizen overwegen om elektronisch voor te gaan schrijven. Vanwege de grote variatie in kosten en effecten tussen verschillende ziekenhuizen is het belangrijk om gegevens te verzamelen uit verschillende settings om tot meer robuuste resultaten te komen. Zoals we hebben aangetoond in onze sensitiviteitsanalyses kunnen verschillen in kosten van het systeem, het implementatie proces en het onderhoudsproces resulteren in verschillende kosten-effectiviteitratio's. Ook de verschillen in incidentie cijfers van medicatiefouten en voorkombare geneesmiddelschade leiden tot variatie in resultaten; in ziekenhuizen waar medicatiefouten frequent voorkomen (kwetsbare en oudere patiënten) zal de balans tussen kosten en effecten positiever uitvallen dan in ziekenhuizen waar minder medicatiefouten plaats vinden. Op basis van onze resultaten kunnen we concluderen dat het voor veel ziekenhuizen kosten-effectief zal zijn om het EVS te implementeren. Zeker wanneer we de investeringskosten om één medicatiefout en één voorkombare bijwerking te voorkomen vergelijken met de extra kosten die gepaard gaan met voorkombare geneesmiddelschade uit de literatuur. Een recent onderzoek, uitgevoerd in de eerste lijn, toonde aan dat een elektronisch voorschrijfsysteem met een ingebouwd formularium medicatiekosten kan reduceren door artsen aan te moedigen generieke en goedkopere geneesmiddelen voor te schrijven. Dit is een andere manier waarop het EVS een bijdrage kan leveren aan de reductie van gezondheidszorgkosten. Toch is het ook in deze situatie belangrijk om aandacht te schenken aan de mening van de voorschrijvers; artsen kunnen mogelijk een negatief oordeel hebben over een systeem dat meer gericht is op reductie van kosten dan verbetering van patiëntenzorg. Bovendien bepaalt de heterogeniteit van de patiëntenpopulatie in welke mate voorschrijvers in staat zijn om volgens het formularium voor te schrijven.

In dit proefschrift hebben we alleen gekeken naar de kosten-effectiviteit van het EVS ten opzichte van het handgeschreven systeem. In de toekomst zal ook de balans tussen kosten en baten van het systeem verder onderzocht moeten

worden. Niet alleen de effecten maar ook de gevolgen van de effecten (minder behandeling, minder gebruik van geneesmiddelen, afname van de lengte van ziekenhuisopname) moeten dan worden meegenomen. Een dergelijke kosten-baten analyse geeft een betere weerspiegeling van de balans tussen kosten en effecten dan alleen een kosten-effectiviteitsanalyse doet. Ons onderzoek is het eerste Nederlandse onderzoek op het gebied van de kosten rondom een EVS en is hopelijk een stimulus voor verdere toekomstige kosten onderzoeken.

Conclusies

We kunnen concluderen dat er momenteel wereldwijd veel gedaan wordt aan het verbeteren van medicatieveiligheid. Het EVS is een (kosten) effectief middel om vooruitgang op het gebied van medicatieveiligheid te bewerkstelligen. Toch moeten deze voorschrijfsystemen nog verder geoptimaliseerd worden om het voorschrijven en toedienen van medicatie in ziekenhuizen zo veilig mogelijk te maken. Dit biedt mogelijkheden voor verder wetenschappelijk onderzoek op het gebied van de kosten en effecten van het EVS, de medicatiebewakingsmodules in het EVS en geavanceerde beslissingsondersteuning zoals klinische beslisregels. Het is noodzakelijk dat dergelijk onderzoek op een betrouwbare wijze wordt uitgevoerd met speciale aandacht voor de methode van het identificeren van medicatiefouten en voorkombare geneesmiddelschade. Dit blijft immers nog steeds een grote uitdaging.

Dankwoord

Groningen, 2009

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Jasperien

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Van Doormaal JE, Mol PGM, van den Bemt PMLA, Zaal RJ, Egberts ACG, Kosterink JGW, Haaijer-Ruskamp FM. *Reliability of the assessment of preventable adverse drug events in daily clinical practice.* Pharmacoepidemiol Drug Saf. 2008 Jul;17(7):645-54.

Van Doormaal JE, van den Bemt PMLA, Mol PGM, Zaal RJ, Egberts ACG, Haaijer-Ruskamp FM, Kosterink JGW. *Medication errors: the impact of prescribing and transcribing errors on preventable harm in hospitalised patients.* Qual Saf Health Care. 2009 Feb;18(1):22-7.

Van Doormaal JE, Mol PGM, Zaal RJ, van den Bemt PMLA, Kosterink JGW, Vermeulen KM, Haaijer-Ruskamp FM. *Computerised Physician Order Entry (CPOE) system: expectations and experiences of users.* Journal of Evaluation in Clinical Practice, in press.

Van Doormaal JE, van de Bemt PMLA, Zaal RJ, Egberts ACG, Lenderink AW, kosterink JGW, Haaijer-Ruskamp FM, Mol PGM. The influence that computerised prescribing has on medication errors and preventable adverse drug events: an interrupted time-series study. Journal of the American Medical Informatics Association (Accepted)

POEMS onderzoeksgroep. *The impact of computerized physician order entry on medication error prevention in hospitalized patients.* Den haag, ZonMw, 2008.

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